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Editorial

Coronary Occlusion and Myocardial Infarction

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It is difficult to realize that at the beginning of the century the syndrome of myocardial infarction had not been recognized and coronary occlusion was regarded as a terminal event—a mere pathologic curiosity. It was later believed that if coronary occlusion did not cause immediate death, it inevitably resulted in myocardial infarction, so that for practical purposes the two were regarded as synonymous; even now we often speak of "coronary thrombosis" when, in fact, we mean myocardial infarction.

It is now realized that this early view was an oversimplification, for detailed studies have revealed an unexpected complexity in the pathologic changes which may result from coronary occlusion. There is, for instance, abundant experimental evidence that if a coronary artery is subjected to gradual narrowing, it may eventually be completely occluded without causing infarction, owing to the concomitant development of a compensatory collateral circulation. Blumgart and his colleagues[1] have convincingly demonstrated the development of such collateral channels in response to coronary occlusions in man, and suggest that, as in experimental animals, coronary occlusions may occur without corresponding infarction.

While it is inherently probable that the myocardial damage caused by occlusion may be reduced by the development of a collateral circulation, the complete prevention of infarction seems to be uncommon, for, in a personal series including 91 occlusions, only 13, all of which had developed distal to pre-existing occlusions, did not result in infarction.[4] Failure of the collateral circulation to prevent infarction in naturally occurring coronary occlusion may be due to two factors. First, the speed with which the artery becomes occluded may outstrip the development of the collateral circulation. Second, even in those instances

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in which a collateral circulation may have had time to develop to the full, the flow of blood through the anastomotic circulation in a diseased heart is likely to be considerably less than that from the healthy arteries of experimental animals, because of the almost inevitable presence of narrowing in the parent vessels.

The result of a coronary occlusion, however, is seldom the simple massive necrosis which is commonly assumed. In fact, it is evident that relatively few infarcts originally consist of homogeneous areas of necrotic myocardium—indeed, if this were so, cardiac rupture would be common. More often patches of necrosis are found intermingled with islands of ischemic, but surviving, myocardium. The presence of surviving muscle within an infarcted area has been described by several authors, including Myers and associates,[2] Wessler and associates,[6] and Prinzmetal and associates,[3] but the implications of this observation and the fate of the living islands of muscle have not been generally appreciated.

During the first few weeks after infarction, further portions of this precariously surviving muscle may undergo necrosis on one or more occasions. Individually, these areas may be large or small, but in the aggregate they often approximate, or even exceed, the size of the original lesion, which may be quite small and possibly asymptomatic, whereas one of the later incidents results in typical symptoms of infarction. Even when the later lesions are smaller than the original, they may still be associated with the typical symptoms and electrocardiographic changes of infarction. Lesions of this type are virtually superimposed upon one another, but occasionally necrosis may spread peripherally into the zone of ischemia which surrounds a recently infarcted area, a process which is probably more in accord with the way in which most clinicians think of extension of an infarct.

It should be emphasized that extension of infarction is not due to extension of the causative occlusion, or to a new occlusion, but to necrosis of already ischemic muscle, so that anticoagulant treatment cannot be expected to prevent it. Extension might be due to extracoronary factors, such as exertion, and it is interesting that in a personal series, only a quarter of the lesions which arose by extension occurred after the patient was at rest in hospital.[5] Since it has been demonstrated that extension is most likely to occur in the first four weeks after the initial lesion, the traditional period of rest after infarction seems to be justified.

The process of extension provides an explanation for the recurrent episodes of pain which may occur during the few weeks after infarction. It may also explain some instances of premonitory pain, for the most obvious clinical symptoms are not necessarily those associated with the first episode of infarction. Alternatively, since several days or weeks may separate successive infarcts resulting from the same occlusion, it is possible that a similar interval may occasionally elapse between the occlusion and the initial infarct. Angina of effort, or mild rest pain, may thus follow the original occlusion whether with or without immediate infarction, whereas a later extension gives rise to the major clinical episode.

In addition to those infarcts just considered which are caused directly or indirectly by coronary occlusions, there are others which may arise quite independently. The diffuse subendocardial infarct which may result from a sudden

fall in coronary blood flow is well known. It is less well known, however, that localized transmural infarcts of the type which usually result from coronary occlusion sometimes occur without any such occlusion, and with only slight narrowing of the corresponding arteries. Presumably, these infarcts are precipitated by one or more extracoronary factors, such as exertion, anemia, hypotension, tachycardia, etc., and the site of the necrosis is determined by localized coronary narrowing. It must be admitted, however, that such extracoronary factors may be far from obvious, and the degree of narrowing may be trivial, so that other factors may sometimes be involved. The most striking feature of these infarcts is their frequency among patients who die suddenly and unexpectedly from coronary disease. For example, in a personal series of cases of sudden death,[7] such infarcts accounted for half the total, compared with only 10 per cent of those in patients observed clinically, and there is as yet no wholly satisfactory explanation of this difference.

The more complex relationship between coronary occlusion and myocardial infarction which has become apparent in recent years is unquestionably due to the use of more detailed methods of examining the heart at postmortem, and there is no doubt that in the past many occlusions and infarcts have been overlooked. The extension of infarcts is especially important in this respect, for as healing takes place, it becomes increasingly difficult to differentiate between adjacent lesions of slightly different ages, until finally the whole area appears homogeneous. Healed, apparently solitary infarcts may thus conceal the existence of several separate incidents. Such factors have contributed to a widespread belief that occlusions and infarcts are usually solitary. This idea seems difficult to correct for there have been many studies—even recent ones—which make the tacit but quite unwarrantable assumption that only one infarct or occlusion is present in each heart. The literature of painless or atypical infarction abounds in examples of this misconception, which may explain in part the extraordinary divergence of opinion as to the frequency of such lesions. The fact that several coronary occlusions and myocardial infarcts may be present in the same heart has an important bearing on many aspects of coronary disease, and although seemingly elementary, it cannot be overemphasized.

REFERENCES

1. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Am. Heart J. **19**:1, 1940.
2. Myers, G. B., Klein, H. A., and Stofer, B. E.: Am. Heart J. **36**:535, 1948.
3. Prinzmetal, M., Kennamer, S. R., Shaw, C. McK., Kimura, N., Lindgren, I., and Goldman, A.: Circulation, **7**:1, 1953.
4. Snow, P. J. D.: Coronary Artery Disease, M.D. thesis, University of Manchester, 1955.
5. Snow, P. J. D., Morgan Jones, A., and Daber, K. S.: Brit. Heart J. **17**:503, 1955.
6. Wessler, S., Zoll, P. M., and Schlesinger, M. J.: Circulation **6**:334, 1952.
7. Snow, P. J. D., Morgan Jones, A., and Daber, K. S.: Unpublished observations.

Clinical Communications

The Vectorcardiogram in Left Ventricular Hypertrophy

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INTRODUCTION

This report discusses the vectorcardiogram of left ventricular hypertrophy and contains a detailed description, both qualitative and quantitative, of the QRS and T loops, and the RS-T junction. The results are compared with those of conventional electrocardiography.[1]

MATERIAL AND METHODS

One hundred nonconsecutive patients with left ventricular hypertrophy were selected from two sources: (1) the medical wards and hypertension outpatient clinic, and (2) patients referred to the laboratory for electrocardiographic study. Patients were included in the series if at least one of the following criteria was fulfilled: left ventricular hypertrophy on physical examination; left ventricular hypertrophy on teleroentgenography and/or fluoroscopy; and a satisfactory etiology for left ventricular hypertrophy such as well-documented hypertension or significant aortic stenosis. Patients with a history of cardiac pain were excluded.

Of the 100 patients selected, 54 fulfilled all three criteria and 45 fulfilled two. In no instance was the electrocardiogram a criterion for admission to or exclusion from the series.

One hundred normal vectorcardiograms previously reported upon from this laboratory were used as controls.[2]

The method of recording and analyzing vectorcardiograms used in this laboratory has been described previously.[2] The terms "initial forces," "body," and "terminal forces" are defined arbitrarily in Fig. 1. It is apparent from Fig. 1 that a vectorcardiogram of which the earliest QRS forces are oriented to the left, anteriorly, and inferiorly has no initial forces in any plane. Fig. 2 illustrates the terms "centrifugal" and "centripetal" as applied to initial forces, body, and terminal appendage.

RESULTS

QRS Loop.—

Horizontal Plane.—The loop tended to be a flattened oval It was oriented to the left, with the long axis lying between +20 and −47 degrees, with a mean of

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−21 degrees. Duration ranged from 0.07 to 0.15 second (Table I). In 97 cases the loops were inscribed entirely counterclockwise, in 2 the loops displayed a cross-over, and in 1 a pinch-off (Fig. 3).

TABLE I. QRS MEASUREMENTS IN THE HORIZONTAL PLANE

	NUMBER OF CASES	MEAN	LARGEST OBSERVATION	SMALLEST OBSERVATION	NUMBER OF CASES ABOVE UPPER LIMIT OF NORMAL	NUMBER OF CASES BELOW LOWER LIMIT OF NORMAL
Initial Forces						
Right*	80	0.05 mv.	0.24 mv.	0.01 mv.	2	0
Anterior*	80	0.04 mv.	0.16 mv.	0.01 mv.	4	0
Number of Time Interruptions†	80	5.5	11	2	1	0
Body						
Width*	100	0.19 mv.	0.70 mv.	0.02 mv.	47	0
Anterior*	99	0.08 mv.	0.28 mv.	0.01 mv.	4	6
Posterior*	100	0.15 mv.	0.70 mv.	0.01 mv.	46	0
Left*	100	0.68 mv.	1.70 mv.	0.03 mv.	30	1
Width*/Left*	100	0.30	1.00	0.05	9	0
Right (IF)*/Left*	80	0.07	0.20	0.01	0	0
Right Terminal Appendage Ratio‡	95	0.21	6.40	0.02	5	0
Terminal Appendage						
Right*	95	0.10 mv.	0.46 mv.	0.01 mv.	8	0
Posterior*	90	0.08 mv.	0.47 mv.	0.01 mv.	17	0
Number of Time Interruptions†	95	9.5	42	2	7	0
Total QRS Duration (Number of Time Interruptions†)						
	100	36.3	60	28	23	0

*Largest displacement.
†Each interruption = 0.0025 second.
‡Ratio of the largest rightward vector of the terminal appendage to the largest leftward vector of the body.
IF = Initial forces.
The values used in Tables I, II, and IV for the upper and lower limit of normal are the single greatest and smallest observations in the 100 controls.

Initial forces: The earliest vectors were oriented to the right in 80 cases and were, therefore, classified as initial forces (Fig. 1). These were inscribed counterclockwise in 76 cases, and the centripetal limb passed anteriorly to the O point. In the remaining 4 cases the centrifugal and centripetal limbs were superimposed, and the centripetal limb passed through the O point. The earliest vectors were

oriented to the left and anteriorly in 20 cases, which, accordingly, were classified as having no initial forces. The various measurements of the initial forces are recorded in Table I.

Body: The various measurements of the body are recorded in Table I.

Terminal appendage. The latest forces of the QRS loop were oriented to the right of the O point in 95 vectorcardiograms, which, therefore, were classified as displaying a terminal appendage. In 61 of the 95 the most rightward point of the terminal appendage was the junction of the QRS loop and the S-T segment (J). The terminal appendage was inscribed counterclockwise in 93 cases; in the remaining 2 there was a crossover, with clockwise inscription of the distal part. The various measurements of the terminal appendage are recorded in Table I.

TABLE II. QRS MEASUREMENTS IN THE SAGITTAL PLANE

	NUMBER OF CASES	MEAN	LARGEST OBSERVATION	SMALLEST OBSERVATION	NUMBER OF CASES ABOVE UPPER LIMIT OF NORMAL	NUMBER OF CASES BELOW LOWER LIMIT OF NORMAL
Initial Forces						
Superior*	27	0.05 mv.	0.14 mv.	0.02 mv.	1	0
Anterior*	27	0.03 mv.	0.06 mv.	0.01 mv.	0	0
Number of Time Interruptions†	27	5.2	12	2	16	0
Body						
Width*	100	0.12 mv.	0.46 mv.	0.01 mv.	28	3
Anterior*	99	0.07 mv.	0.22 mv.	0.01 mv.	12	5
Posterior*	86	0.12 mv.	0.40 mv.	0.01 mv.	18	0
Inferior*	100	0.46 mv.	1.75 mv.	0.02 mv.	1	15
Width*/Inferior*	100	0.36	1.75	0.04	22	0
Superior(IF)*/Inf.*	27	0.08	0.31	0.01	1	0
Superior Terminal Appendage Ratio‡	93	2.06	36.6	0.01	45	0
Terminal Appendage						
Posterior*	90	0.15 mv.	0.66 mv.	0.02 mv.	43	0
Superior*	93	0.33 mv.	1.70 mv.	0.01 mv.	46	0
Number of Time Interruptions†	93	16.7	42	2	34	0
Total QRS Duration (Number of Time Interruptions†)						
	100	36.6	60	28	23	0

*Largest displacement.

†Each interruption = 0.0025 second.

‡Ratio of the largest superior vector of the terminal appendage to the largest inferior vector of the body.

IF = Initial forces.

Sagittal Plane.—The QRS loops were smooth in contour, variable in shape, and usually inscribed clockwise. Inscription was entirely counterclockwise in 5 cases. In some cases there was sudden reversal in the direction of inscription, or crossovers occurred. Duration of the QRS loop ranged from 0.07 to 0.15 second.

Initial forces: Initial forces were present in 27 cases. They were inscribed clockwise in 24, and were superimposed in 3. The centrifugal limb moved anteriorly in most of the 27 cases, and went straight up in the remaining few. The various measurements of the initial forces are listed in Table II.

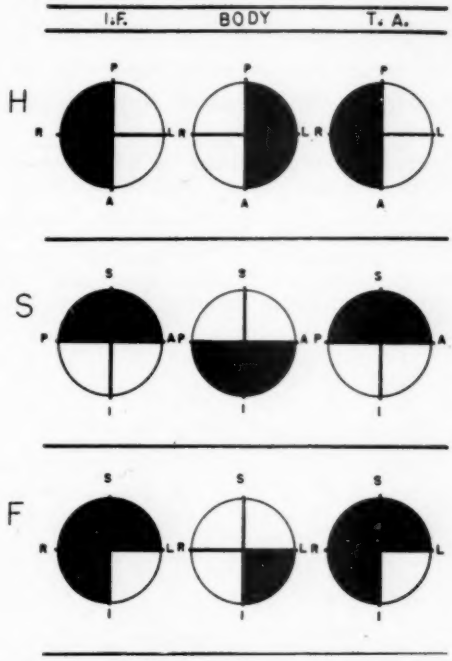

Fig. 1.—Arbitrary subdivisions of QRS loop indicated in black. *I.F.* = Initial forces. *T.A.* = Terminal appendage. In this and the following figures, *H* = horizontal plane projection, *S* = sagittal plane projection, *F* = frontal plane projection, *A* = anterior, *P* = posterior, *I* = inferior, *S* = superior, *R* = right, and *L* = left, as seen on patient facing the observer.

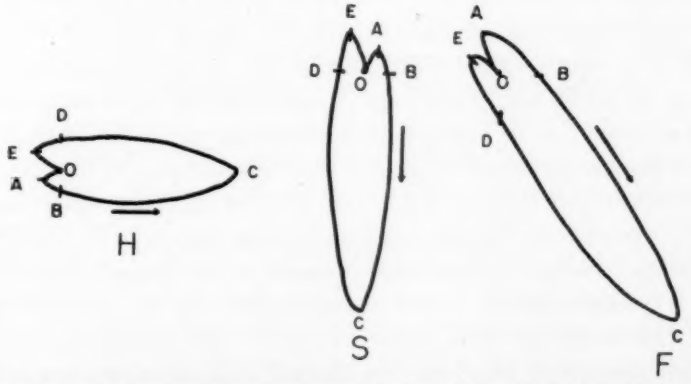

Fig. 2.—Definition of centrifugal and centripetal limbs of the QRS loop. *O* = point of origin of cardiac vectors. *OA* = centrifugal limb and *AB* the centripetal limb of the initial forces. *BC* = centrifugal limb and *CD* = the centripetal limb of the body. *DE* = centrifugal limb and *EO* = the centripetal limb of the terminal appendage.

Body: The direction of inscription of the body was entirely clockwise in 82 cases, entirely counterclockwise in 7, and mixed in the rest. The various measurements of the body are recorded in Table II.

Terminal appendage: A terminal appendage was noted in 93 cases. It was inscribed clockwise in 76, counterclockwise in 7, and crossed over in 10. As stated above, the body in 7 of the 100 cases was counterclockwise. Each of these had a terminal appendage which greatly exceeded the body in size, and its early portion was anterior to the O point. In half of the remaining loops with terminal appendages (86 cases), terminal forces were partly anterior to the O point, J being the most anterior point in all but 3. Of the 7 cases with a counterclockwise terminal appendage, the body was counterclockwise in 5 and clockwise in 2. The various measurements of the terminal appendage are given in Table II.

TABLE III. DIRECTION OF INSCRIPTION OF THE QRS LOOP IN RELATION TO ANGLE α IN THE FRONTAL PLANE (TYPE-A CASES ONLY)

ANGLE α	ENTIRELY CLOCKWISE	ENTIRELY COUNTER-CLOCKWISE	CLOCKWISE WITH CROSSOVER IN DISTAL PORTION	COUNTERCLOCKWISE WITH CROSSOVER IN DISTAL PORTION	TOTAL
$\leq$ +10	0	3	0	0	3
+11 to +15	0	2	0	0	2
+16 to +20	1	2	1	1	5
+21 to +25	1	5	1	1	8
+26 to +30	0	3	0	2	5
+31 to +35	0	1	0	0	1
+36 to +40	1	3	1	0	5
+41 to +45	0	3	1	0	4
+46 to +50	1	2	0	0	3
+51 to +55	1	1	0	2	4
+56 to +60	2	0	1	0	3
$\geq$ +61	2	4	2	1	9
Total					52

Frontal Plane.—Although the loops displayed great variability, all but 4 could be classified into three basic patterns (Fig. 4). The 52 cases of Type A were clockwise, counterclockwise, or mixed; the 33 Type-B and the 11 Type-C loops were all inscribed counterclockwise. Initial forces were present in 49 cases of Type A, 22 of Type B, and 7 of Type C. A terminal appendage was present in 99 cases, being absent in 1 Type-A vectorcardiogram. The Type-B loop usually presented a downward concavity in the centrifugal limb of the body (Fig. 4,*B*). The QRS duration was 0.07 to 0.15 second. The direction of inscription of the QRS loop of Type A for different angles alpha is shown in Table III.

Initial forces: Initial forces were present in 80 cases.* They were counterclockwise in 61, clockwise in 9, and superimposed in 10. Various measurements of the initial forces are listed in Table IV.

Body: Inscription of the body in the 52 Type-A cases was clockwise in 9, counterclockwise in 29, and mixed in 14. Only a small portion of the loop repre-

*Two of the cases were among the four not classified as Types A, B, or C.

sents the body and initial forces in the Type-B cases, the remainder being the terminal appendage. The body was inscribed counterclockwise in all 33, but in 3 of these, clockwise inscription occurred distal to a crossover. The body in every Type-C case was entirely counterclockwise. Various measurements of the body are given in Table IV.

TABLE IV. QRS MEASUREMENTS IN THE FRONTAL PLANE

	NUMBER OF CASES	MEAN	LARGEST OBSERVATION	SMALLEST OBSERVATION	NUMBER OF CASES ABOVE UPPER LIMIT OF NORMAL	NUMBER OF CASES BELOW LOWER LIMIT OF NORMAL
Initial Forces						
Superior*	27	0.05 mv.	0.14 mv.	0.01 mv.	1	0
Right*	80	0.05 mv.	0.22 mv.	0.01 mv.	2	0
Number of Time Interruptions†	80	5.8	12	2	1	0
Body						
Width*	100	0.44 mv.	1.40 mv.	0.01 mv.	63	1
Inferior*	100	0.46 mv.	1.75 mv.	0.03 mv.	1	15
Left*	100	0.67 mv.	1.66 mv.	0.01 mv.	28	5
Greatest Vector of the Body	100	0.82 mv.	2.00 mv.	0.03 mv.	3	9
Width*/Greatest Vector of the Body	100	0.59	1.10	0.06	45	0
Terminal Appendage						
Superior*	93	0.34 mv.	1.74 mv.	0.01 mv.	46	0
Right*	95	0.10 mv.	0.48 mv.	0.01 mv.	8	0
Maximum Vector	99	0.47 mv.	1.80 mv.	0.03 mv.	61	0
Width**	81	0.46 mv.	1.30 mv.	0.03 mv.	55	0
Number of Time Interruptions†	99	16.2	45	2	39	0
Total QRS Duration (Number of Time Interruptions†)						
	100	37.1	60	28	34	0

*Largest displacement.
**The width was zero or could not be measured in 19 cases.
†Each interruption = 0.0025 second.

Terminal appendage: The terminal appendage was inscribed in a counterclockwise direction in all of the Type-B and Type-C cases; clockwise inscription distal to a crossover occurred in 2 cases of each type. The duration and magnitude of the terminal forces tended to be large in Type-B and Type-C loops. The various measurements of the terminal appendage are listed in Table IV.

J.—The QRS loop was closed in 5 cases, and the position of J could not be ascertained in 3 others. The spatial orientation and magnitude of J was recorded in the remaining 92 cases. The position of J is summarized in Table V. The maximal magnitude of J was 0.27 mv.

T Loop.—The T loops varied considerably in size, shape, and spatial orientation. Their configuration was oval or arc shaped in half of the cases, narrow with superimposition of the two limbs in many, and small and round in a few. Inscription was generally counterclockwise in the horizontal and frontal planes, and clockwise in the sagittal projection. The T vectors varied in magnitude from very small to a maximum of 0.47 mv. The orientation of the greatest T-loop vector is summarized in Fig. 5. The QRS-T angles are depicted in Fig. 6.

TABLE V. LOCATION OF RS-T JUNCTION (J) IN REFERENCE TO "O" POINT

	RIGHT			O			LEFT		
	ANTERIOR	O	POSTERIOR	ANTERIOR	O	POSTERIOR	ANTERIOR	O	POSTERIOR
Superior	16	11	5	0	1	0	0	0	0
O	7	8	2	0	5	0	0	0	0
Inferior	23	13	3	1	1	0	1	0	0

The position of J could not be determined in 3 cases.

DISCUSSION

Previous studies[3-5] of the vectorcardiogram in left ventricular hypertrophy have furnished detailed descriptions of the QRS loop, S-T junction, and T loop with which our findings are in agreement. Burch and collaborators[3] have shown that these morphologic features provide a basis for the vectorcardiographic diagnosis of left ventricular hypertrophy. The superior performance of the electrocardiogram in their series was attributed to the method of case selection. This view is supported by the results in the present series in which in no instance was the electrocardiogram a criterion for admission to or exclusion from the series. Duchosal and associates[5] concluded that the large surface area of the loops was the main feature of left ventricular hypertrophy, but presented no data on normal values. The present study, although concerned with a detailed descriptive characterization, bases the diagnosis of left ventricular hypertrophy on various measurements of the QRS loop.

The method of selecting patients had as its aim the collection of a group of cases in which it could be felt with confidence that each patient had left ventricular hypertrophy. Right ventricular hypertrophy may have been present in some cases. An attempt was made to exclude by careful clinical evaluation those patients with angina pectoris or myocardial infarction. Our observations, and the conclusions stemming from them, therefore, are concerned almost exclusively with alterations in the electrical phenomena of the heart beat which characterize left ventricular hypertrophy.

The initial forces in vectorcardiograms of left ventricular hypertrophy may be entirely normal, they may be small though oriented normally, they may be absent, the downward component may be larger than normal. When they are normal in size and orientation, or in orientation alone, they help to distinguish

Fig. 3.—Illustration of crossover (*left*) and pinch-off (*right*) in the QRS loop.

Fig. 4.—The three morphologic types of frontal plane QRS loops in left ventricular hypertrophy.

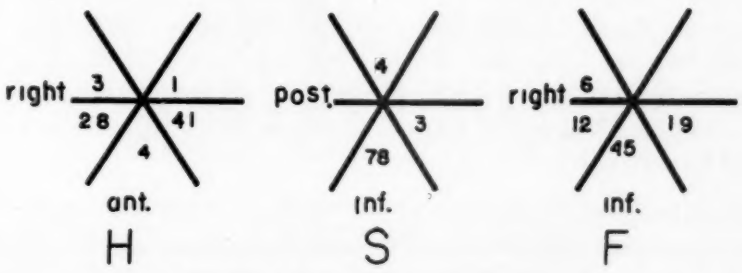

Fig. 5.—Orientation of the largest T vector. Numerals indicate the number of cases. *Ant.* = Anterior. *Post.* = Posterior. *Inf.* = Inferior.

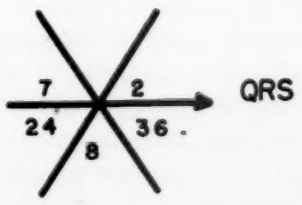

Fig. 6.—Numerals indicate the number of cases in which the greatest T-wave vector falls within each sextant when the QRS loop in the horizontal plane is rotated so that its greatest vector occupies a standard position.

between normal and left ventricular hypertrophy, on the one hand, and myocardial infarction, on the other. The distinction between normal loops and those of left ventricular hypertrophy cannot be made on the basis of orientation of initial forces, but the downward component in left ventricular hypertrophy may exceed the normal. This is often accompanied by a small rightward component, and this combination is expressed in the scalar electrocardiogram as large Q_{AVL} and small or inapparent q_{V6}. In 20 per cent of our cases the earliest forces were oriented to the left; these, too, have absent q_{V6}. In 15 of these 20 cases the loops displayed a horizontal position in the frontal plane, thus accounting for the orientation of the earliest forces. In other words, left-anterior-down orientation of the earliest forces may be due to left bundle branch block or, in its absence, to horizontal position and counterclockwise rotation, positional and rotational changes which in themselves suggest left ventricular hypertrophy. The differentiation of left bundle branch block from left ventricular hypertrophy with earliest forces directed left, anteriorly, and inferiorly depends upon other features of the QRS loop: e.g., rightward displacement of the terminal appendage beyond the J occurs in left ventricular hypertrophy but not in left bundle branch block. Both of these have to be distinguished from normals, of which 3 per cent have earliest forces left, anteriorly, and inferiorly.

The paucity of diagnostic clues for left ventricular hypertrophy in the initial forces is striking, especially when compared to the abundance of such signs in the body and terminal appendage. The maximum leftward displacement of the body of the QRS loop was abnormal in 30 cases, and the maximum posterior displacement was abnormal in 46 cases. One and/or the other of these measurements was excessive in 60 cases, and they must be considered important signs of left ventricular hypertrophy. Although posterior displacement greater than normal also occurs in anterior myocardial infarction, it tends to occur earlier in the QRS loop in infarction than in left ventricular hypertrophy[6] (Fig. 7). Clockwise inscription of the QRS loop in the horizontal plane, and completely posterior position of the QRS loop occur in anterior infarction but not in left ventricular hypertrophy.

Another problem is the distinction between left ventricular hypertrophy and inferior myocardial infarction. The maximum duration of superiorly oriented early forces in normal individuals varies according to angle alpha in the frontal plane from zero at angles of 35 degrees or less to a maximum of 0.0275 second at more than 55 degrees. In inferior myocardial infarction, early superior forces of greater than normal duration occur[7]; and it is necessary to know whether similarly prolonged early forces occur in uncomplicated left ventricular hypertrophy. Of the 27 cases of left ventricular hypertrophy with initial superior forces, 16 exceeded the normal by a mean of 0.0125 second, with a range of 0.0025 to 0.0175 second. Thus, a diagnosis of inferior myocardial infarction from a loop diagnostic of left ventricular hypertrophy should be based upon other criteria, namely, the sweep and magnitude of the superior early forces. In this way the problem of differential diagnosis in inferior myocardial infarction and left ventricular hypertrophy is resolved.

The terminal forces were oriented to the right in 95, and superiorly in 93 of our 100 cases of left ventricular hypertrophy, compared to 55 and 59, respectively, in 100 normal individuals. The maximum superior component of the terminal appendage was abnormal in 46 cases, and the greatest terminal appendage vector in 61. One and/or the other of these measurements was excessive in 62 cases. The maximum superior component was considered abnormal when it exceeded the maximum value found in a series of 100 normal individuals previously studied.[2] Subsequent experience with normal individuals, however, has shown that the maximum superior component of the terminal appendage rarely may exceed the upper limit of normal established in the earlier study.

In left ventricular hypertrophy, diagnostic signs are more conspicuous toward the end than at the beginning of the QRS loop, and consist for the most part of potentials which are larger than normal in a rightward, superior, and posterior direction. The tendency for smaller than normal initial forces to occur in left ventricular hypertrophy has been mentioned. Another measurement which, when smaller than normal, favors the diagnosis of left ventricular hypertrophy is the maximum inferior vector of the body of the QRS loop; this was less than the lower limit of normal in 15 cases (Tables II and IV). It is this tendency to small inferior and large superior components which results in the characteristic morphology of the QRS loop in left ventricular hypertrophy (Fig. 4, Types B and C).

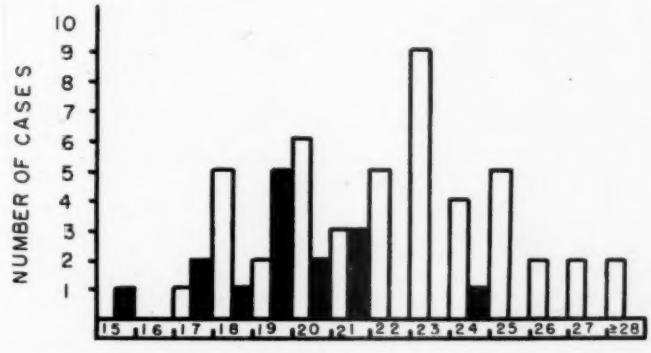

Fig. 7.—Cases with abnormal posterior displacement (greater than 0.13 mv.),[2] showing the time interval in the QRS loop when the maximum displacement occurs. Solid blocks = anterior myocardial infarction.[6] Open blocks = left ventricular hypertrophy. Abscissa = number of time interruptions from the beginning of the QRS loop to the maximum posterior displacement.

Abnormalities in the S-T junction, T loops, and QRS-T angle occur in most of the cases of left ventricular hypertrophy. J was displaced to the right in 91 per cent of the entire series, compared to 3 per cent of the normal controls; the T loop was oriented to the right in about 40 per cent of the cases in which this analysis was possible, but not in a single normal individual; in many cases, the morphology of the T loop was abnormal. The horseshoe-shaped configuration of the T loop has been reported by others.[3] The QRS-T angle in a majority of the cases was abnormal (Fig. 6). Certainly these abnormalities must be considered an important feature of the vectorcardiogram in left ventricular hypertrophy. Their diagnostic significance, however, is minimized by the fact that a multi-

plicity of factors influences the spatial position of J and the configuration and orientation of the T loop. For these reasons, abnormalities of J and T should be accorded less weight than those of QRS in the diagnosis of left ventricular hypertrophy.

STATISTICAL CONSIDERATIONS

The greatest help in solving a diagnostic problem is obtained, as a rule, from a study of those variables which are frequently abnormal in the condition under consideration, but which are normal in other conditions. Eleven of the 42 QRS measurements (Tables I, II, IV) studied in this investigation fulfilled these criteria (Fig. 8). The frequency of abnormality for each of these 11 measurements is shown in Table VI and Fig. 9,*A* and *B*. Fig. 10 indicates the number of abnormalities in each case when all 42 QRS measurements are used.

TABLE VI. MEASUREMENTS CHARACTERISTICALLY ABNORMAL IN LEFT VENTRICULAR HYPERTROPHY*

	GREATEST VALUE FOUND IN 100 NORMAL CASES	NUMBER OF CASES OF LVH EXCEEDING SUCH A VALUE	MEAN PLUS 2 SIGMAS OF 100 NORMAL CASES	NUMBER OF CASES OF LVH EXCEEDING SUCH A VALUE
Horizontal Plane				
1. Leftward body	0.83 mv.	30	0.68 mv.	46
2. Body width	0.16 mv.	47	0.14 mv.	63
3. Posterior body	0.13 mv.	46	0.10 mv.	69
4. Posterior appendage	0.13 mv.	17	0.11 mv.	25
Sagittal Plane				
5. Body width	0.16 mv.	28	0.14 mv.	39
6. Posterior body	0.16 mv.	18	0.10 mv.	46
7. Posterior appendage	0.13 mv.	43	0.09 mv.	61
Frontal Plane				
8. Leftward body	0.82 mv.	28	0.65 mv.	47
9. Body width	0.30 mv.	63	0.25 mv.	69
10. Width appendage	0.29 mv.	55	0.19 mv.	64
11. Greatest vector of body	1.58 mv.	3	1.36 mv.	8

*See Fig. 8.

Statistically, the accuracy of the vectorcardiogram as a diagnostic test for left ventricular hypertrophy will depend on the values chosen as the upper limit of normal and the number of measurements considered. If mean plus two standard deviations is used as the upper limit of normal, the following results are observed: When all 11 measurements are used, 92 per cent of the cases of left ventricular hypertrophy and 24 per cent of the normal cases will have at least one abnormal measurement. If only one measurement is used, 69 per cent of the cases

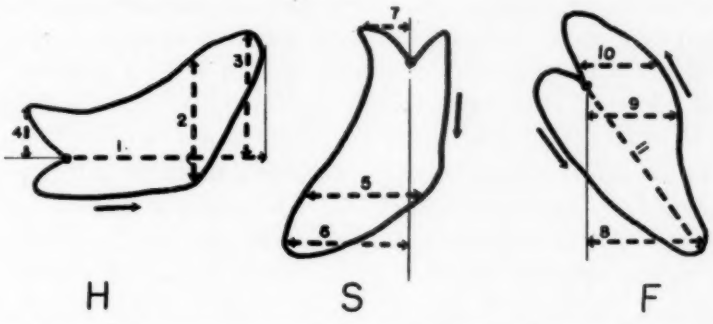

Fig. 8.—Eleven QRS measurements useful in the diagnosis of left ventricular hypertrophy. See Table VI.

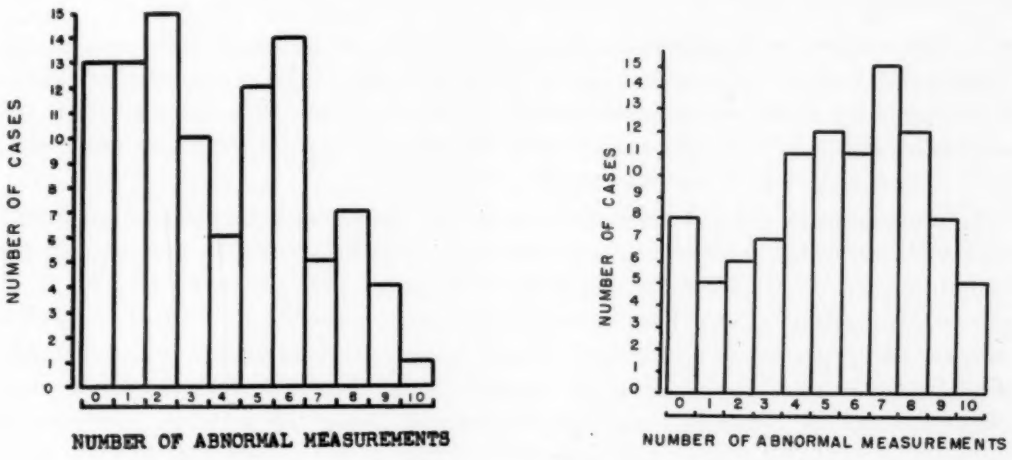

Fig. 9.—Number of abnormal measurements of the QRS loop in each case of left ventricular hypertrophy. Only the 11 measurements which are abnormal almost exclusively in left ventricular hypertrophy are included. *A*, Using greatest value as upper limit of normal. *B*, Using the mean plus two standard deviations as upper limit of normal.

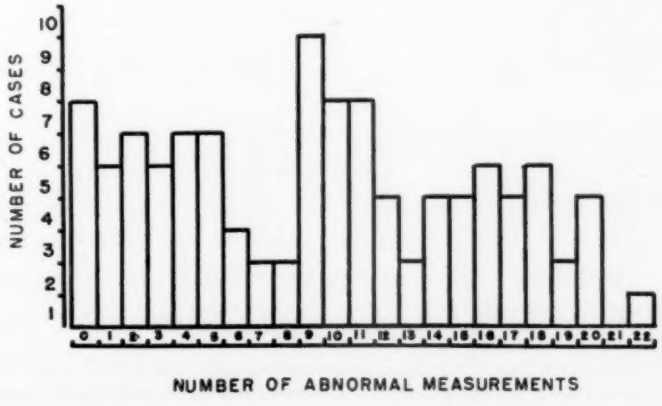

Fig. 10.—Number of abnormal measurements of the QRS loop in each case of left ventricular hypertrophy. All 42 measurements are included.

of left ventricular hypertrophy and 2.5 per cent of the normal cases will exceed the upper limit of normal. When 3 of the 11 measurements are used, the vectorcardiogram displays its greatest accuracy, in that with a positive diagnosis in 91 per cent of the cases of left ventricular hypertrophy, there is overdiagnosis in only 7.3 per cent of the normal cases. In other words, when 3 instead of all 11 measurements are used, correct positive diagnosis declines only 1 per cent (from 92 to 91 per cent), whereas the incidence of false positive results declines from 24 to 7.3 per cent.* These 3 measurements are the maximum leftward vector of the body in the horizontal plane, the maximum posterior vector of the body in the horizontal plane, and the maximum width of the terminal appendage in the frontal plane (Fig. 8, Nos. *1*, *3*, *10*).

COMPARISON OF VECTORCARDIOGRAPHIC† AND ELECTROCARDIOGRAPHIC DIAGNOSES

The electrocardiographic findings in the present series of 100 cases of left ventricular hypertrophy were studied in detail and will be reported separately.[1] The upper limits of normal selected[8-11] for the various QRS measurements are shown in Table VII. A diagnosis of left ventricular hypertrophy was made if at least one measurement was abnormally large.

The diagnosis of left ventricular hypertrophy was made by electrocardiogram and vectorcardiogram in 71 cases, and was missed by both in 6 cases. Of the remaining 23 cases, 20 were diagnosed by vectorcardiogram alone, and 3 by electrocardiogram alone. The vectorcardiographic criteria used to diagnose left ventricular hypertrophy correctly in 91 per cent of our cases obligated a calculated overdiagnosis of 7.3 per cent of normal cases. The electrocardiogram overdiagnosed 15 per cent of our normal controls, using the criteria necessary to achieve 74 per cent correct diagnosis of the cases of left ventricular hypertrophy. In other words, the vectorcardiogram reduces underdiagnosis of left ventricular hypertrophy by 65 per cent at the same time that it reduces overdiagnosis of normal cases by 50 per cent.

TABLE VII. UPPER LIMIT OF NORMAL OF VARIOUS MEASUREMENTS OF THE ELECTROCARDIOGRAM*

AGE	LEWIS INDEX (8)	R_{AVL} (9)	S_{V1} (9)	S_{V2} (9)	R_{V5} (9, 7)	R_{V6} (9)	S_{V1} PLUS R_{V5} OR R_{V6} (11)
15–20	17	5.8	25.1	45.5	26.0	24.4	40
20–25	17	7.6	26.2	39.2	26.0	22.6	40
25–30	17	7.6	26.2	39.2	26.0	22.6	35
30–40	17	7.6	26.2	39.2	26.0	22.6	35
Over 40	17	10.1	20.0	25.4	20.7	19.0	35

*Values in tenths of a millivolt.

*The rate of diagnosis is based on the sample under study; the rate of overdiagnosis is calculated from the theorem of combined probability. Since the variables under study are not entirely independent, the theoretical percentages of overdiagnosis are only approximate.

†The vectorcardiographic diagnosis of left ventricular hypertrophy is based on 3 measurements only, as discussed above.

THE O POINT IN LEFT VENTRICULAR HYPERTROPHY

The superiority of the vectorcardiogram is all the more impressive because the method of case finding tended to introduce a bias in favor of the electrocardiogram. This superiority, moreover, is evident in ways other than the diagnostic score. If serial electrocardiograms are obtained in patients with left ventricular hypertrophy, confusing day-to-day changes may be noted. These occasionally lead to an erroneous diagnosis of myocardial infarction (Fig. 11). A simultaneous series of vectorcardiograms will not disclose variations corresponding to those in the electrocardiogram, and a diagnostic error is avoided. This discrepancy can be explained by the configuration of the QRS and T loops in left ventricular hypertrophy, and the difference in the reference systems used in the two methods of examination. Slight changes in the positions of the vectorcardiographic electrodes will not alter significantly the relation of the electrodes to the O point, whereas equally small shifts of the precordial electrodes may do so when the electrodes are near the O point.[12] If the QRS loop has a large terminal appendage, rightward displacement of J, and an arc-shaped T loop oriented to the right and inferiorly, the recorded potentials will vary according to the position of the precordial electrodes. An upward shift of the V_6 electrode or a downward shift of the O point will change an rS deflection, depressed S-T segment, and upright T wave to a qR deflection, elevated S-T segment, and inverted T wave (Fig. 11).

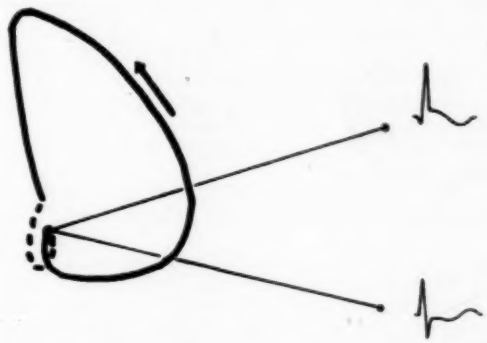

Fig. 11.—QRS changes in V_6 resulting from a change in position of the precordial exploring electrode.

SUMMARY

The vectorcardiograms and electrocardiograms of 100 patients with left ventricular hypertrophy were studied in detail. The method of selecting patients insured the presence of left ventricular hypertrophy and absence of clinically evident coronary disease.

The QRS and T loops, and S-T junction (J) were analyzed.

The morphology of the QRS loops was described, and numerous measurements were made.

The configuration and orientation of the T loop and its relation to the QRS loop were noted.

Position of the S-T junction was noted.

A screening diagnosis of left ventricular hypertrophy can be made on the basis of QRS morphology, S-T segment displacement, T-wave configuration and orientation, QRS-T angle, and certain features of the initial forces and terminal appendage.

A definitive diagnosis of left ventricular hypertrophy can be made on the basis of 11 QRS measurements which are frequently abnormal in left ventricular hypertrophy but only infrequently abnormal in other conditions. As a rule, more than one such abnormal measurement is present in each case.

A diagnosis of left ventricular hypertrophy was made in 91 per cent of 100 cases of uncomplicated left ventricular hypertrophy, using only 3 of the 11 diagnostic measurements.

The vectorcardiogram is superior to the electrocardiogram for the diagnosis of left ventricular hypertrophy.

REFERENCES

1. Wolff, R., Mazzoleni, A., and Wolff, L.: The Electrocardiogram in Left Ventricular Hypertrophy. (In preparation.)
2. Young, E., Wolff, L., and Chatfield, J.: The Normal Vectorcardiogram. I, AM. HEART J. **51**:713, 1956.
3. Horan, L. G., Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: The Spatial Vectorcardiogram in Left Ventricular Hypertrophy, Circulation **10**:728, 1954.
4. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
5. Lamb, L. E., Grosgurin, J. R., and Duchosal, P. W.: Vectorcardiographic Studies of Ventricular Hypertrophy, Cardiologia **28**:65, 1956.
6. Karlen, W. S., Wolff, L., and Young, E.: The Vectorcardiogram in Anterior Myocardial Infarction. III, AM. HEART J. **52**:45, 1956.
7. Young, E., Wolff, L., and Karlen, W.: The Vectorcardiogram in Inferior Myocardial Infarction. IV, AM. HEART J. **52**:232, 1956.
8. Sodi-Pallares, D., and Calder, R. M.: New Bases of Electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
9. Vaquero, M., Limon, R. L., and Limon, A. L.: Electrocardiograma normal, Estudio de 500 casos en derivaciones standard y unipolares, Arch. Inst. cardiol. México **17**:155, 1947.
10. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, AM. HEART J. **37**:161, 1949.
11. Grubschmidt, H. A., and Sokolow, M.: The Reliability of High Voltage of the QRS Complex as a Diagnostic Sign of Left Ventricular Hypertrophy in Adults, AM. HEART J. **54**:689, 1957.
12. August, T., Mazzoleni, A., and Wolff, L.: Positional and Respiratory Changes in Precordial Lead Patterns Simulating Acute Myocardial Infarction, AM. HEART J. **55**:706, 1958.

Assessment of Mitral Regurgitation by Indicator Dilution: Observations on the Principle of Korner and Shillingford

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Indicator dilution curves have been shown to have a lowered peak concentration and a disproportionate prolongation of the disappearance slope in the presence of valvular incompetence.[1] This distortion of dilution curves has permitted the derivation of several useful semiquantitative indices which usually differentiate predominant stenosis and regurgitation.[1] However, either a very low cardiac output or a large volume diluting the indicator may produce similar alterations of dilution curves. Furthermore, accurate assessment of valvular lesions requires quantification of valvular regurgitation. In 1955 and 1956, Korner and Shillingford[2,3] proposed a statistical approach to quantification based on their studies of indicator dilution curves in a circulatory model, which suggested that the effect of regurgitation could be distinguished from the effects of flow and volume. Treating the dilution curve as a frequency distribution of dye particles, and regarding the effect of regurgitation as a diminished probability of forward movement of a given dye particle, they attempted to assess this probability as a function of the dispersion of the curve. Choosing either the variance[3] or the reciprocal of the slope of the descending limb[2] as the expression of dispersion, they demonstrated in their model that each of these consisted of a component largely determined by flow and another largely determined by the volume between the sites of injection and collection. With valvular incompetence, both the variance and the reciprocal of the slope increased and could be mathematically separated into components related to forward flow, volume, and regurgitant flow. Since their studies with the model had shown that the conventional methods of calculation gave correct results for flow and volume whether or not regurgitation was present, they could, by means of regression equations

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relating either the variance or the reciprocal of the slope to flow and volume, calculate the parameter expected in the absence of regurgitation. They then described the diminished probability of forward flow as the ratio of the expected variance or reciprocal of the slope to the value observed from the dilution curve. In the model, the application of this principle was shown to quantify regurgitation accurately. Since the alterations in dilution curves in the presence of valvular incompetence were qualitatively similar in man and in the model, this statistical approach was applied to patients with valvular disease. The necessary regression equation was based on a series of curves obtained, in the absence of regurgitation, following the injection of dye into peripheral vein, right atrium, or pulmonary artery. The cardiac output and "central" volume were calculated from each dilution curve as described by Hamilton.[4]

In the original work, estimates of regurgitant flow were obtained by both the slope and variance methods in a series of 5 patients with clinical diagnoses of pure stenotic valvular lesions and in a series of 12 patients with mixed lesions including tricuspid, mitral, or aortic insufficiency, or a combination of these. In the former group the reported estimates of regurgitant flow were 0.0 L./min. in each case, and in the latter group the values ranged from 1.8 to 8 L./min. However, the degree of correspondence between the estimates of regurgitant flow and any other assessment of the severity of the valvular incompetence was not reported.

Others have applied the Korner and Shillingford methods to the problem of assessing mitral regurgitation, but either the correlations with other estimates of the severity of the lesion[5] or the regurgitant flow values[1] have not been reported. Hence, the methods of Korner and Shillingford have not been subjected to the rigorous clinical testing which any method, proved only in a model, requires before clinical and physiologic acceptance.

The present study was undertaken to evaluate critically the basic premise of the slope and variance methods. Since the observations were limited to patients with isolated mitral valvular disease, the severity of mitral regurgitation could be reliably graded by surgical and specific clinical criteria, and these grades of severity could be correlated with the results of the variance method. This has permitted a test, in man, of the validity of the principle that valvular regurgitation determinably alters the parameters of dilution curves independently of the effects of flow and volume. Furthermore, data from these patients have afforded a method of evaluating the accuracy of the calculated mitral regurgitant flow.

METHODS AND MATERIALS

Two groups of adult patients were studied. The first comprised 25 patients with no clinical evidence of valvular incompetence and with no palpable regurgitant jet in those in whom surgery was performed. Of these patients, 12 had pure mitral stenosis; 6 had pure aortic stenosis; 2 had combined mitral and aortic stenosis; 3 had aortic stenosis of no physiologic significance[6]; 1 had no heart disease; and 1 had bronchogenic carcinoma without heart disease. The 30 dilution curves obtained in this group of patients provided the data from which a revised regression equation was derived.

The second group was composed of the 5 patients without valvular disease and the 12 patients with mitral stenosis from Group I, plus 45 patients who had mitral stenosis and regurgitation,

pure or combined, as their only valvular lesion. These patients were classified by two systems of grading the severity of mitral regurgitation. The first was the conventional five-category schema[1] in which the classifications were: normal (*N*), no physiologically detectable valvular disease; pure mitral stenosis (*MS*); mitral stenosis and regurgitation, with the former predominating (*MSmr*); combined regurgitation and stenosis with predominant regurgitation (*MRms*); and essentially pure mitral regurgitation (*MR*). The criterion for inclusion in a given group was the presence and severity of a regurgitant jet palpated by a surgeon, except in those patients in whom evidence of predominant or essentially pure mitral regurgitation was considered unequivocal and in whom surgery was not performed.

This system, although useful, has several disadvantages. The exclusion of patients with mild disease in whom surgery was not considered may bias the results of any analysis because the entire spectrum of mitral valvular disease is not represented. Moreover, at least in this series, surgery has been at the hands of several different surgeons, with the resulting possibility of inequality of a given grade of regurgitation for different patients. Furthermore, the agreement between estimates by different surgeons in the same case has occasionally been poor. Finally, surgical palpation may be performed at a time when blood pressure and cardiac output are grossly different from the conditions prevailing during cardiac catheterization.

In an attempt to extend and stabilize the clinical estimate, we have formulated a second system in which medical criteria are used in those cases in which surgery was not performed, and both medical and surgical criteria in those cases which came to operation. As presently applied, the result is a scale of 1-10 in which each point represents the presence of an objective clinical sign or operative finding, each of which constitutes some evidence for mitral incompetence.[7] Palpatory, electrocardiographic, or fluoroscopic evidence of left ventricular enlargement each contributed one point. The absence of an opening snap, lack of accentuation of the apical first sound, and apical pansystolic murmur of Grade 3 or louder (on the basis of a scale of 1-6), a "giant" (4+) left atrium, and systolic expansion of the left atrium each represented one point. The operative finding was the surgeon's estimate of the mitral regurgitant jet as slight (1-2+) or marked (3-4+), with assignment of one or two points, respectively. If systemic hypertension was present, one point was subtracted from those contributed by left ventricular enlargement. The points for each patient were added and the total treated as a numerator. A denominator of 8 was used for patients who were not surgically explored, and a denominator of 10 was used for patients who were subjected to left atrial exploration. Each value was then multiplied by 10 for simplicity of expression. In this way, patients may have maximal scores of 10 with or without surgery. The validity and applicability of this system of classification are dependent upon the fact that physiologic study in each case excluded the presence of other valvular disease, so that each clinical sign could be attributed to mitral pathology. This clinical scale appears to have practical advantages in a disease which must be a continuum of severity and in which there is no absolute standard of comparison. Although neither the clinical nor the surgical scale represents the desired absolute standard, they both provide relatively stable indices of mitral regurgitation which correlate well with each other ($r = 0.82$).

All of the patients were studied by transdorsal percutaneous catheterization of the left side of the heart.[8] The left atrium was entered with two (No. 16 or No. 18) thin-walled needles, and a catheter was advanced into the left ventricle. Left atrial and left ventricular pressures were recorded, usually simultaneously, with strain gauge manometers (Statham P23D), on a direct-writing oscillograph (Sanborn). Mean mitral diastolic pressure gradients were computed by integrating several cycles of graphically superimposed left atrial and left ventricular pressure tracings. The mitral diastolic filling period was defined as the interval between the points of equalization of the left atrial and left ventricular pressures. The heart rates were obtained from simultaneously recorded electrocardiograms. Mitral diastolic valvular areas were computed according to the Gorlins' formula,[9] using a discharge coefficient (C) of 1.0, as empirically determined in this laboratory. Indicator dilution curves were obtained by injecting 4 to 5 mg. of Evans blue dye from calibrated pipettes[10] rapidly through the left atrial needle, followed immediately by a saline flush. The dilution curves were obtained from the brachial artery with one of two techniques. In the first, arterial blood was drawn at a constant rate of 0.7 c.c./sec. through 40 cm. of polyethylene tubing (I.D., 1.13 mm.) into a cuvette densitometer.[11] The output of

this densitometer was recorded continuously on the oscillograph. An integrated sample technique was used for the calibration of these dilution curves.[12] With the second technique, arterial blood flowed from a cannula at a rate of 1 to 2 c.c./sec. through 30 cm. of polyethylene tubing (I.D., 3 mm.) into heparinized test tubes mounted on a rotating disk. Funnels in the test tubes permitted continuous collection without spillage between samples. The complete cycle of the 24 tubes could be regulated to give a filling period of 1.25 to 2.0 seconds per tube. Concentrations of dye in plasma were determined in a spectrophotometer (Beckman model DU) at a wave length of 625 millimicra. Hematocrits were determined by centrifuging heparinized whole blood for 30 minutes in Wintrobe tubes at 2,500 r.p.m., with a centrifuge arm radius of 15 cm. A plasma-trapping factor of 4 per cent[13] was used in calculating the proportion of plasma present in the packed red cell portion. All curves were plotted on semilogarithmic paper and the concentrations extrapolated to 1 per cent of peak concentration value. The cardiac outputs were calculated according to the method of Hamilton,[4] and the "central" volume was calculated as the product of cardiac output and mean circulation time. The variance of dilution curves and the estimates of regurgitant flow, in liters per minute, were calculated as described by Korner and Shillingford.[3] In addition, for reasons to be discussed, a revised regression equation relating variance to flow and volume was derived from the data of the first group of patients, using standard mathematical methods, and this equation was also used to obtain estimates of regurgitant flow.

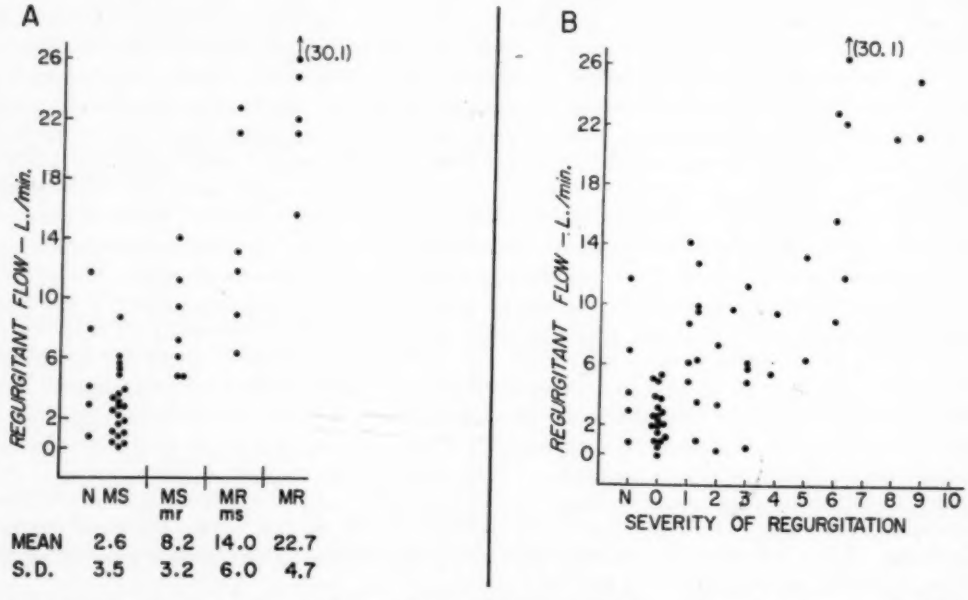

Fig. 1.—Regurgitant flows calculated using the original regression equation of Korner and Shillingford[3] (log predicted variance = 2.6069 − 2.219 log CO + 1.995 log V) plotted against the surgical (*A*) and clinical (*B*) classifications of mitral valvular disease. The correlation coefficients are 0.86 (*A*) and 0.80 (*B*).

RESULTS

The data obtained in both series of patients are given in Table I.

Fig. 1, *A* and *B*, shows the regurgitant flows, in liters per minute, obtained using the original regression equation of Korner and Shillingford plotted against the surgical and clinical classifications, with 44 and 56 observations, respectively. The most noteworthy point is that there are satisfactory correlations between the variance method values and the clinical and surgical estimates of the severity of mitral regurgitation. However, the group of patients without surgical evi-

dence of regurgitation have calculated regurgitant flows averaging 2.6 L./min., with a large amount of scatter about the mean. The average value in the patients with essentially pure mitral regurgitation is 22.7 L./min., and the maximum value is 30.1 L./min. For reasons discussed below, it is apparent that these results are excessively large. This fact indicated that, although theoretically justifiable, it is empirically incorrect to apply the original regression equation of Korner and

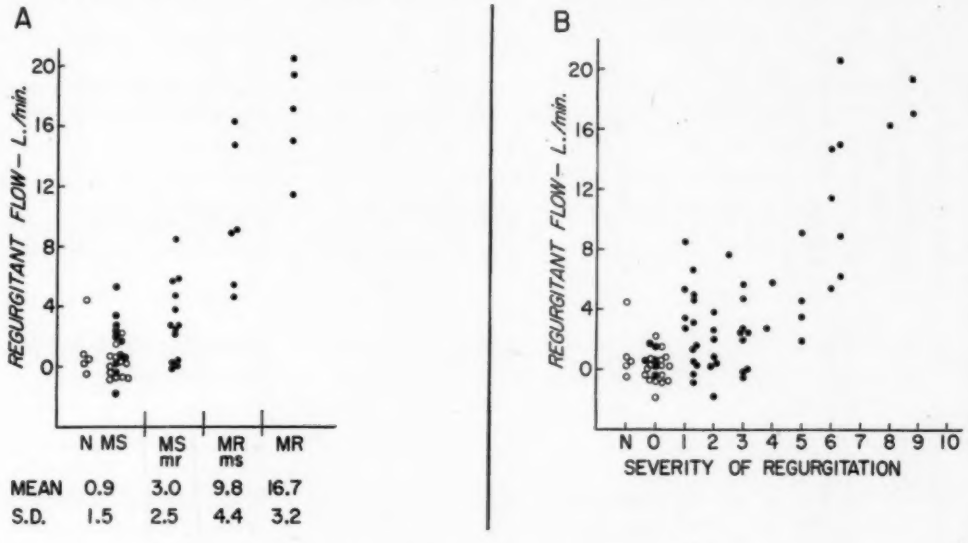

Fig. 2.—Regurgitants flows calculated using the revised regression equation plotted against the surgical (*A*) and clinical (*B*) classifications of mitral valvular disease. The patients whose data were used in the derivation of the regression equation (Table I,*B*) are represented by open circles. All other patients with isolated mitral valvular disease (Table I,*C*) are shown by solid circles. Correlation coefficients for the solid circle data are 0.80 (*A*) and 0.77 (*B*). Correlation coefficients for all data shown are 0.86 (*A*) and 0.79 (*B*).

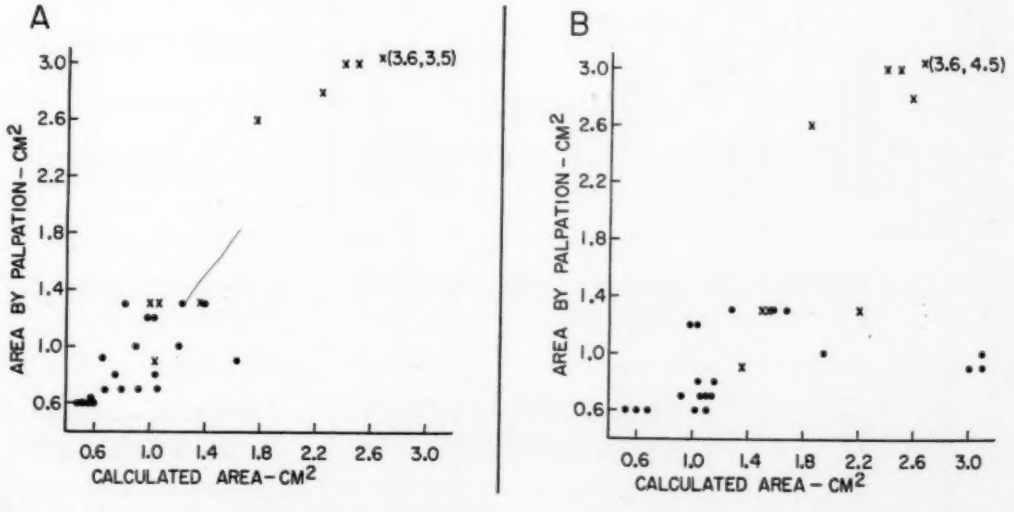

Fig. 3.—Mitral valvular diastolic area calculated without (*A*) and with (*B*) the regurgitant flow estimate, plotted against the area described by the surgeon. Note the frequent, gross overestimates of calculated area when the regurgitant flow, defined by the variance method, is used in the computation (*B*). Correlation coefficients are 0.91 (*A*) and 0.67 (*B*).

TABLE I. DATA FROM PATIENTS IN GROUP I (PARTS *A* AND *B*) AND GROUP II (PARTS *B* AND *C*)

NUMBER	AGE, SEX	B.S.A. ($M.^2$)	PHYSIOLOGIC DIAGNOSIS	CARDIAC OUTPUT (L./MIN.)	CENTRAL VOLUME (L.)	OBSERVED VARIANCE	KORNER-SHILLINGFORD EQUATION		REVISED EQUATION	
							EXPECTED VARIANCE	REGURGITANT FLOW (L./MIN.)	EXPECTED VARIANCE	REGURGITANT FLOW (L./MIN.)
A.										
56	46, M	1.88	AS	9.62	1.14	3.30	.....	....	.....	....
73	60, M	1.75	AS	6.51	0.84	4.88	.....	....	.....	....
79	45, M	1.79	AS-MS	7.74	0.65	3.23	.....	....	.....	....
81	28, F	1.38	AS-MS	7.34	0.70	3.36	.....	....	.....	....
14A	50, M	1.77	AS	4.83	0.48	3.74	.....	....	.....	....
14A	50, M	1.77	AS	3.61	0.54	7.25	.....	....	.....	....
34A	63, M	1.97	AS	8.20	0.48	2.31	.....	....	.....	....
37A	48, M	1.87	AS	6.55	0.53	2.97	.....	....	.....	....
46A	30, F	1.60	AS	5.40	0.41	2.27	.....	....	.....	....
B.										
			CLASSIFICATION							
			SURGICAL	CLINICAL						
121	54, M	1.87	N	N	5.82	0.69	5.84	3.91	2.9	5.66	0.2
122	57, M	2.12	N	N	9.52	0.63	2.41	1.08	11.7	1.64	4.5
130	48, M	1.78	N	N	3.96	0.52	6.31	5.24	0.8	7.26	−0.5
39A	46, M	1.54	N	N	10.03	0.68	1.90	1.12	6.9	1.77	0.8
41A	25, F	1.39	N	N	6.05	0.38	1.79	1.07	4.1	1.65	0.5
57	54, F	1.76	MS	0	5.67	1.27	20.69	13.87	2.8	18.72	0.6
71	46, F	1.70	NO	0	6.07	1.33	16.53	12.56	1.9	17.69	−0.4
71	46, F	1.70	NO	0	6.99	1.40	10.66	10.65	0.0	14.50	−1.9
88	44, M	1.53	MS	0	3.78	0.64	9.81	8.73	0.5	11.88	−0.7
90	22, F	1.45	MS	0	7.10	0.70	3.99	2.55	3.9	3.83	0.3
91	49, M	1.90	NO	0	4.41	0.77	13.00	8.97	2.0	12.09	0.3

92	57, M	1.68	MS	O	4.76	0.73	8.07	6.78	0.9	9.44	−0.7
99	49, F	1.39	MS	O	3.09	0.63	12.51	8.26	1.6	17.41	−0.9
99	49, F	1.39	MS	O	3.24	0.61	14.92	11.19	1.1	14.90	0.0
107	41, F	1.62	MS	O	3.52	0.41	7.08	4.11	2.5	5.88	0.7
107	41, F	1.62	MS	O	3.19	0.28	3.04	2.34	1.0	3.44	−0.4
110	44, M	1.54	MS	O	3.53	0.31	3.69	2.40	1.9	3.54	0.2
126	46, M	2.02	NO	O	7.65	0.66	3.23	1.94	5.1	2.94	0.8
127	50, F	1.34	MS	O	5.29	0.42	3.46	1.80	5.0	2.70	1.5
127	50, F	1.34	MS	O	8.00	0.64	2.29	1.65	3.1	2.54	−0.8
32A	30, F	1.35	MS	O	6.23	0.37	1.99	1.07	5.3	1.47	2.2
					C.						
31	37, M	1.88	MR	6	4.20	1.27	127.8	26.82	15.6	34.61	11.4
32	48, F	1.44	MRms	5	3.04	1.13	134.8	44.51	6.3	54.10	4.6
38	57, M	1.74	MR	6.3	7.07	2.02	88.38	21.21	22.1	28.30	15.0
43	21, F	1.40	MSmr	3	4.02	0.71	20.06	9.19	4.8	12.71	2.4
44	42, F	1.78	MSmr	3	7.29	1.04	13.59	5.30	11.2	7.62	5.7
55	53, M	1.72	MRms	6	6.60	1.57	65.66	14.43	22.8	20.29	14.7
60	52, M	1.88	NO	1.3	6.62	0.73	8.11	3.24	9.9	4.78	4.6
61	48, M	1.74	MS	0	6.03	1.60	26.36	19.24	2.2	25.51	0.2
63	49, F	1.52	MS	1	4.67	0.67	17.79	6.23	8.7	8.36	5.3
64	33, M	1.85	MRms	8	4.59	1.73	230.9	41.56	21.1	50.81	16.3
74	45, F	1.63	MRms.	6	5.36	1.22	39.17	14.88	8.9	19.56	5.4
75	54, M	1.85	MS	3	6.02	0.97	9.28	8.54	0.5	9.93	−0.4
80	50, F	1.52	MR	8.8	3.25	1.29	369.6	48.05	21.2	59.16	17.1
83	54, M	1.82	MS	3	6.61	0.79	7.19	3.88	5.7	5.54	2.0
84	37, F	1.64	MR	8.8	4.85	2.44	442.0	70.72	24.9	88.41	19.4
85	26, F	1.46	MSmr	1	6.40	0.80	14.03	4.21	14.1	6.04	8.5
93	43, M	1.72	MS	2	5.07	0.75	10.19	6.22	3.3	8.76	0.8
93	43, M	1.72	MS	2	6.69	1.05	6.83	6.56	0.3	9.29	−1.8
98	46, M	1.71	MSmr	2	3.99	0.63	20.13	7.25	7.2	10.25	3.8
104	50, F	1.62	NO	3.8	4.20	0.61	14.24	6.27	5.4	8.69	2.7
105	41, M	1.69	NO	1.3	5.31	0.50	4.05	2.47	3.5	3.68	0.5
106	47, M	1.68	MSmr	4	4.93	0.94	30.81	10.47	9.4	14.17	5.8
108	45, F	1.30	MSmr	1	2.61	0.37	19.02	6.66	4.8	9.32	2.7
111	48, M	1.80	MSmr	3	4.93	0.57	8.52	3.83	6.1	5.54	2.7
112	32, M	1.91	MR	6.3	6.87	1.52	69.51	13.21	30.1	17.38	20.6
115	47, F	1.91	NO	1.3	6.36	0.73	10.51	3.51	12.7	5.15	6.6
115	47, F	1.91	NO	1.3	4.78	0.65	12.43	5.35	6.3	7.59	3.1

TABLE I. DATA FROM PATIENTS IN GROUP I (PARTS *A* AND *B*) AND GROUP II (PARTS *B* AND *C*)—Cont'd

NUMBER	AGE, SEX	B.S.A. ($M.^2$)	PHYSIOLOGIC DIAGNOSIS		CARDIAC OUTPUT (L./MIN.)	CENTRAL VOLUME (L.)	OBSERVED VARIANCE	KORNER-SHILLINGFORD EQUATION		REVISED EQUATION	
								EXPECTED VARIANCE	REGURGITANT FLOW (L./MIN.)	EXPECTED VARIANCE	REGURGITANT FLOW (L./MIN.)
					C.—Continued						
117	47, M	1.81	MRms	5	4.46	1.24	88.80	22.20	13.1	29.31	9.1
119	50, M	1.69	MS	1	3.41	0.47	15.97	5.75	6.1	7.98	3.4
124	41, F	1.65	MRms	6.3	2.80	0.83	146.5	27.84	11.8	35.20	8.9
140	52, F	1.43	NO	2.5	6.30	1.18	24.10	9.40	9.7	11.57	7.7
141	54, F	1.68	MS	0	5.20	0.88	12.53	8.14	2.8	11.15	0.6
141	54, F	1.68	MS	0	4.13	0.75	18.70	9.91	3.7	13.28	1.7
12A	51, F	1.64	NO	1.3	6.96	1.44	26.70	11.21	9.5	15.49	5.0
28A	31, F	1.55	NO	1.3	4.64	0.42	2.84	2.39	0.9	3.52	−0.9
142	48, F	1.49	MSmr	3	3.63	0.86	21.94	.....	....	22.67	−0.1
142	48, F	1.49	MSmr	3	5.34	1.06	28.36	.....	....	15.02	4.7
143	34, M	1.93	MSmr	3	4.03	0.94	21.55	.....	....	21.45	0.0
146	41, M	1.91	NO	1.3	4.79	0.70	8.24	.....	....	8.66	−0.3
148	26, F	1.58	MSmr	2	4.52	0.48	7.01	.....	....	4.80	2.1
150	53, F	1.35	NO	1.3	1.97	0.24	10.02	.....	....	7.45	0.6
150	53, F	1.35	NO	1.3	2.32	0.28	8.51	.....	....	5.32	1.4
152	50, M	1.58	MS	2	5.02	0.77	14.42	.....	....	9.40	2.7
154	55, F	1.41	MS	3	3.32	0.44	13.40	.....	....	7.76	2.4
157	49, F	1.38	NO	1.3	5.13	0.50	5.23	.....	....	4.03	1.5
158	45, F	1.42	MSmr	2	3.22	0.90	34.03	.....	....	31.53	0.2
158	45, F	1.42	MSmr	2	2.85	0.77	34.64	.....	....	30.38	0.4
159	52, M	1.88	NO	5	8.64	1.57	16.42	.....	....	11.63	3.5
159	52, M	1.88	NO	5	10.73	1.75	10.70	.....	....	9.13	1.9
161	32, F	1.57	NO	0	2.65	0.39	15.50	.....	....	9.92	1.5
162	61, F	1.54	NO	0	2.34	0.41	17.05	.....	....	13.87	0.6
162	61, F	1.54	NO	0	2.66	0.47	11.74	.....	....	13.45	−0.4
163	57, M	1.94	NO	6.3	4.39	1.49	112.1	.....	....	42.71	6.2

NO = No operation.

Shillingford to data which are obtained by different techniques and which, with left atrial injections, include a smaller range of volumes than were encountered with injections on the right side of the heart. It was for this reason that a new regression equation was derived, relating variance to cardiac output and "central" volume, from the data given in parts *A* and *B* of Table I.

The regression equation is:

$$\log EVx = 2.6303 - 2.0637 \log CO + 1.8799 \log V,$$

where *EVx* is the variance expected for the prevailing flow and volume; *CO* is cardiac output, in liters per minute; and *V* is the product of cardiac output and mean circulation time, in liters.

New values for expected variance were computed with this regression equation and are shown in parts *B* and *C* of Table I along with the corresponding values for regurgitant flow, in liters per minute. The latter values are plotted against the surgical and clinical scales in *A* and *B* of Fig. 2. Correlation coefficients are given both including and excluding the patients with mitral valvular

TABLE II. MITRAL DIASTOLIC AREAS AS DETERMINED BY CALCULATION FROM HEMODYNAMIC DATA AND BY PALPATION AT TIME OF MITRAL VALVULOPLASTY

NUMBER	SYSTEMIC CARDIAC OUTPUT (L./MIN.)	TOTAL LEFT VENTRICULAR OUTPUT (L./MIN.)	MITRAL VALVULAR AREA (CM.²)		
			CALCULATED, USING SYSTEMIC CARDIAC OUTPUT	CALCULATED, USING TOTAL LEFT VENTRICULAR OUTPUT	SURGEONS' ESTIMATE
43	4.02	6.4	0.68	1.10	0.7
44	7.29	13.0	1.63	3.12	0.9
57	5.67	6.3	1.40	1.55	1.3
61	6.03	6.2	1.06	1.10	0.7
63	4.67	10.0	0.91	1.95	1.0
64	4.59	20.9	0.66	3.01	0.9
71*	6.07	6.1	2.40	2.40	3.0
71*	6.99	7.0	2.50	2.50	3.0
75	6.02	6.0	1.04	1.04	0.8
83*	6.61	8.6	1.04	1.36	0.9
85	6.40	14.9	1.31	3.05	1.0
88	3.78	3.8	0.60	0.60	0.6
90	7.10	7.4	1.23	1.28	1.3
92	4.76	4.8	0.92	0.92	0.7
93*	5.07	5.9	2.23	2.59	2.8
98	3.99	7.8	0.56	1.10	0.6
99	3.09	3.1	0.98	0.98	1.2
99	3.24	3.2	1.03	1.03	1.2
106*	4.93	10.7	1.00	2.20	1.3
107	3.52	4.2	0.57	0.68	0.6
107	3.19	3.2	0.52	0.52	0.6
108	2.61	5.3	0.50	1.02	0.6
110*	3.53	3.7	1.76	1.85	2.6
111	4.93	7.6	0.75	1.16	0.8
119	3.41	6.8	0.82	1.64	1.3
127*	5.29	6.8	3.48	4.47	3.6
141*	5.20	5.8	1.36	1.51	1.3
141*	4.13	5.8	1.07	1.51	1.3
32A	6.23	8.4	0.80	1.08	0.7

*Postoperative mitral valvular area estimates, compared with postoperative catheterization results.

disease from whom the equation was derived. As shown, the previously noted correlations have been essentially unaffected by the use of a regression equation derived specifically for use with dilution curves obtained after injection into the left atrium. However, in the group with surgically absent regurgitation, the average calculated regurgitant flow is 0.9 L./min. using the new equation, as compared to 2.6 L./min. when the original regression equation of Korner and Shillingford was used. In the group with the most severe mitral regurgitation the calculated regurgitant flows average 16.7 L./min. using the new equation, as compared with 22.7 L./min. using the original equation.

This magnitude of calculated regurgitant flows seemed unreasonably large even in the absence of an absolute standard for comparison. The accuracy of the results has been evaluated by including the calculated regurgitant flow as part of the total mitral diastolic flow in the Gorlins' hydraulic formula[9] for computing the mitral diastolic orifice area. These data are given in Table II. The diastolic mitral valvular areas have been calculated for each of these patients, using first the systemic cardiac output, or flow past the aortic valve, and second the sum of systemic cardiac output and regurgitant flow, or total estimated left ventricular output. In other words, the mitral valvular areas were computed first on the assumption of no regurgitation, and second on the assumption that the estimates of regurgitant flow were accurate. The results have been plotted in Fig. 3,*A* and *B* against planimetric measurements of the valvular area diagrammed after mitral surgery. Even though absent or trivial mitral regurgitation was found at surgery in most of the patients in this group, this analysis conclusively demonstrates that the calculated valvular area, when the estimate of regurgitant flow is incorporated in the total diastolic flow, is frequently far in excess of the area found at operation. Therefore, the variance method, even when adapted for use with left atrial injection data, frequently yields gross overestimates of regurgitant flow.

DISCUSSION

The principle described by Korner and Shillingford[3,4] has remained one of the most promising approaches to the quantification of valvular regurgitation, but the slope and variance methods have not had wide acceptance. Among the reasons for the failure of the methods to attain wider acceptance are the rather lengthy computations involved, a reluctance to apply to man a method the efficacy of which has been proved only in a circulatory model, and the fact, demonstrated above, that the use of different injection sites and different techniques may require the derivation of different regression equations.

Hoffman and Rowe[14] recently have extended the original observations of Korner and Shillingford and have reported work which challenges the clinical use of the slope and variance methods. Using a different circulatory model, they demonstrated that varying the size, shape, or elasticity of the proximal chamber entered by the regurgitant jet altered the parameters of dilution curves. Moreover, these changes were independent of the magnitude of regurgitation. This work suggests that the Korner and Shillingford principle may apply to a

given model system or to a given type of patient, but that in certain instances, changes other than the quantity of regurgitation in the circulatory system under study may invalidate the results. Although variations as extreme as those introduced in the model probably never occur in patients, it is theoretically conceivable that even less extreme differences in left atrial characteristics might invalidate the application of the slope or variance methods to some patients with mitral valvular disease.

The present work has elucidated three aspects of the clinical use of the variance method. First, the theoretical applicability of the original regression equation to data obtained with different injection sites was not borne out. In large part this is probably related to the smaller volumes encountered with left atrial injections, as compared with those found by Korner and Shillingford using injections on the right side of the heart. However, it is likely that the collection of dilution curves with a cuvette densitometer or with timed fractional samples rather than with the less precise ear oximeter has also been a factor.

Second, the variance method, when applied to dilution curves obtained after left atrial injections, leads to overestimates of regurgitant flow. For this reason, the actual numerical values have little physiologic meaning except as a useful scale by which the severity of mitral regurgitation may be assessed in a given patient relative to a group of patients.

Finally, it has been shown that the variance method gives results which correlate well with either clinical or surgical estimates of the severity of mitral regurgitation. These satisfactory correlations have two implications. The basic principle of Korner and Shillingford, that alterations in dilution curves greater than those predicted for the prevailing flow and "central" volume are attributable to valvular regurgitation, is valid. Furthermore, these correlations imply that variation in the severity of regurgitation, within the group of patients studied, accounts for most of the variation in the values for regurgitant flows. The latter strongly suggests that the left atrial pressure-volume characteristics have had little effect on the dilution curves, and, therefore, that the factors studied by Hoffman and Rowe must be regarded as theoretical limitations which ordinarily do not play a significant role in the presence of mitral disease.

The demonstration of the validity of the basic principle of the variance method, combined with the fact that, as presently applied, the method frequently gives overestimates of regurgitant flow, provides grounds for further work with the principle in an attempt to obtain quantitative physiologic results in man. Meier and Zierler[15] have demonstrated that the "central" volume, estimated as the product of cardiac output and mean circulation time, includes the volume between injection and collection sites plus the volume of all temporally equivalent pathways. Since volume can only influence dilution curves when it is volume with which the sampled indicator has mixed, the "central" volume is probably inappropriate for use with the variance and slope methods. This consideration of the volume requirements of the Korner and Shillingford methods suggests that these methods may be improved by the use of a volume estimate which is more closely related to the mixing phenomenon.

SUMMARY

The variance method of Korner and Shillingford for the quantification of valvular regurgitation has been subjected to clinical study. The results of the method correlate well with carefully defined surgical and clinical scales of the severity of mitral regurgitation in patients with isolated mitral valvular disease. Thus, the basic principle of Korner and Shillingford is valid: mitral regurgitation determinably alters the parameters of indicator dilution curves independently of the effects of flow and "central" volume. However, even after the derivation of a regression equation suited to the techniques used and to the range of volumes encountered with injections into the left atrium, the variance method grossly overestimates the regurgitant flow in many patients. For this reason, the results are a useful means of grading the severity of mitral regurgitation in a given patient with reference to a group of patients, but the calculated numerical values do not represent actual regurgitant flows. An analysis of the requirements of the variance method suggests that the validity of the basic principle may be preserved and more physiologic results obtained by the use of a volume which is more closely related to the mixing phenomenon.

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REFERENCES

1. Marshall, H. W., Woodward, E., Jr., and Wood, E. H.: Hemodynamic Methods for Differentiation of Mitral Stenosis and Regurgitation, Am. J. Cardiol. **2**:24, 1958.
2. Korner, P. I., and Shillingford, J. P.: The Quantitative Estimation of Valvular Incompetence by Dye Dilution Curves, Clin. Sc. **14**:553, 1955.
3. Korner, P. I., and Shillingford, J. P.: Further Observations on the Estimation of Valvular Incompetence From Indicator Dilution Curves, Clin. Sc. **15**:417, 1956.
4. Kinsman, J. M., Moore, J. W., and Hamilton, W. F.: Studies on the Circulation. I. Injection Method: Physical and Mathematical Considerations, Am. J. Physiol. **89**:322, 1929.
5. Dexter, L., Novack, P., Schlant, R. C., Phinney, A. O., Jr., and Haynes, F. W.: Mitral Insufficiency, Tr. A. Am. Physicians **70**:262, 1957.
6. Hancock, E. W., Madison, W. M., Proctor, M. H., Abelmann, W. H., and Starkey, G. W. B.: Aortic Stenosis of No Physiologic Significance, New England J. Med. **258**:305, 1958.
7. Carleton, R. A., Levinson, G. E., Katznelson, G., Stein, S. W., and Abelmann, W. H.: Clinical and Physiologic Assessment of Mitral Incompetence. Proc. New England Cardiovascular Soc. **17**:28, 1959.
8. Fisher, D. L.: The Use of Pressure Recordings Obtained at Transthoracic Left Heart Catheterization in the Diagnosis of Valvular Heart Disease, J. Thoracic Surg. **30**:379, 1955.
9. Gorlin, R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves, and Central Circulatory Shunts, Am. Heart J. **41**:1, 1951.
10. Robinson, C. V., Li, T. H., and Etsten, B. E.: Improved Injection Pipettes for Determination of Cardiac Output by Dye Method, J. Lab. & Clin. Med. **42**:773, 1953.
11. Gilford, S. R., Gregg, D. E., Shadle, O. W., Ferguson, T. B., and Marzetta, L. A.: An Improved Cuvette Densitometer for Cardiac Output Determination by the Dye Dilution Method, Rev. Sc. Instr. **24**:696, 1953.
12. McNeely, W. F., and Gravallese, M. A.: Measurement of Cardiac Output by Dye Dilution Technique: Use of an "Integrated" Sample Collection in Calibration of the Photometric Instrument, J. Appl. Physiol. **7**:55, 1954.
13. Owen, C. A., and Power, M. H.: Intercellular Plasma of Centrifuged Human Erythrocytes by Means of Iodo^{131}-Albumin, J. Appl. Physiol. **5**:323, 1952.
14. Hoffman, J. I. E., and Rowe, G. G.: Some Factors Affecting Indicator Dilution Curves in the Presence and Absence of Valvular Incompetence, J. Clin. Invest. **38**:138, 1959.
15. Meier, P., and Zierler, K. L.: On the Theory of the Indicator Dilution Method for Measurement of Blood Flow and Volume, J. Appl. Physiol. **6**:731, 1954.

Diagnostic Value of the Left Atrial Pressure Pulse in Mitral Valvular Disease

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Difficulty is frequently encountered in the selection of suitable candidates for mitral valve surgery. In this regard, numerous features of the left atrial pressure pulse have been employed in attempts to separate "pure" mitral stenosis from mitral stenosis with significant mitral insufficiency or "pure" mitral insufficiency. The aim of this study was to correlate some aspects of the left atrial pressure pulse with the state of the valve as determined at the time of surgery. It was found that formulae involving the slope of the initial portion of the *y* descent, coupled with the presence or absence of "catheter washout" from the left ventricle in its systole, provided the most satisfactory assessment of the state of the mitral valve.

METHODS AND MATERIAL

The analysis of 54 left atrial pressure pulse tracings from 43 patients, all but one of whom had rheumatic mitral valvular disease, forms the basis of this report. Thirty-six tracings were recorded directly at surgery and 18 by left heart catheterization via the posterior percutaneous approach.[1] In 11 cases, tracings were recorded both at left heart catheterization and at the time of thoracotomy.

Earlier tracings were obtained with transducer manometers and a Sanborn direct-writing apparatus. Subsequently, strain gauge manometers and a photographic recorder were used.† The left atrial pressure pulses were examined for various features proposed by other workers as indicative of mitral stenosis or mitral insufficiency. This was done without prior knowledge of the surgical findings in order to avoid bias. After complete analysis the results were compared with the surgical judgment. At least five representative pulse cycles in each tracing were studied, corresponding to a complete respiratory cycle or to a period of suspended breathing. Pulse cycles which appeared to contain artefact were avoided. The various measurements made in the selected pulse cycles from each tracing were averaged. Left ventricular pressure pulses were also recorded consecutively or simultaneously in many cases. The zero reference level was placed 5 cm. from the sternal angle in the anteroposterior diameter.

Surgical exploration of the mitral valve was carried out in all of the cases included in the study, except in 5 which clinically were classic examples of pure mitral insufficiency. The valves were

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evaluated in all operated cases, 85 per cent by the same surgeon. The cases were divided into three groups according to mitral valve size and presence or absence of a regurgitant jet as estimated at surgery, except in Group III (see below). The limitations inherent in evaluating the mitral valve by palpation at the time of surgery were taken into account.

Group I.—Thirty-two patients were thus classified as having significant mitral stenosis with, at most, insignificant mitral insufficiency or none at all. In this group the mitral valve orifices had been reported by the surgeon to be 1 cm. or less in diameter, or, when slit-like, from 1 to 2 cm. in length; none had significant regurgitant jets. Six of these patients had associated aortic valvular lesions and/or grossly elevated left ventricular diastolic pressures. The diagnosis of aortic stenosis was confirmed directly in 3 patients by the presence of a systolic pressure gradient across the aortic valve, and in another by autopsy. One patient had classic auscultatory evidence of aortic insufficiency in addition to elevated left ventricular end-diastolic pressure. Apparent left ventricular failure was present in the sixth patient, but the nature of any additional aortic valvular lesion was not determined.

Group II.—Four patients were considered to have a combination of both significant mitral stenosis and significant mitral insufficiency, in that the valve orifices were somewhat larger than those of the patients in Group I, although definitely stenosed, and a marked regurgitant jet was present.

Group III.—One patient was classified as having significant mitral insufficiency with, at most, an insignificant mitral stenosis, the valve being described by the surgeon as "patulous with marked regurgitation." Five others, not operated upon, were included in this group because of clear-cut clinical evidence of pure mitral regurgitation. Another patient was included here because of the deductions made from his left atrial curve (see below), despite the fact that clinically he was considered to have mitral stenosis, but at surgery proved to have chronic nonspecific myocarditis with left ventricular failure and no organic mitral valve deformity.

Before proceeding further, the features of atrial pulse contour should be defined. The atrial pulse consists of a series of waves, with ascending and descending limbs, peaks, and troughs. The successive positive waves in each cycle are labeled a, c, and v. The a wave is due to atrial activity; the c wave is related to phenomena occurring at the instant of closure of the A-V valve. The onset of the ascending limb of the c wave is called the z point and marks end-diastolic pressure in the atrium. The descending limb of the c wave is called the x descent, and ends at the x trough. The ascending limb of the v wave is related to atrial filling while the A-V valve is closed. Its peak, which occurs close to the time that the A-V valve opens, is called the v point. The descending limb of the v wave is called the y descent. The point at which this descent ceases is the y point. The curve, which in diastole normally mirrors ventricular pressure, may then continue to the next a wave as a practically horizontal line (isotonic trough), or rise more or less slowly (h ascent). If the heart rate is rapid, diastole is shortened, and these latter two phenomena may be cut off. Under certain circumstances, other features of the curve may be obscured or absent. The various features may be identified by timing with the simultaneously recorded electrocardiogram (cf. Fig. 5). The above terminology will be adhered to in this report.

RESULTS

The left atrial pressure level was elevated and an end-diastolic pressure gradient across the mitral valve was present in all of the patients of Groups I and II*. However, a definite gradient was also present in 2 of the 6 patients with pure mitral insufficiency, including the one who was operated upon (Fig. 1).

The a wave was often absent because of the frequent occurrence of atrial fibrillation in chronic mitral valvular disease. Proper analysis of this wave was not possible because of the small number of patients in this series who had sinus rhythm. Alterations in the c wave were not constant; in some patients of Group III the c wave was almost indiscernible, and, of course, so was the x descent.

*For footnote see opposite page.

However, our over-all results show, in agreement with others,[2] that the x descent is also frequently diminished or absent in cases of pure mitral stenosis associated with atrial fibrillation. In addition, the presence of a pronounced x descent did not exclude significant mitral regurgitation, as was also previously reported.[3]

The absolute height of the v wave in our series was of no aid in differentiating valvular lesions; this is in accord with other reports.[3] As shown in Fig. 2, subtracting the height of the c wave from that of the v point[4] did not clearly separate the groups in this series.

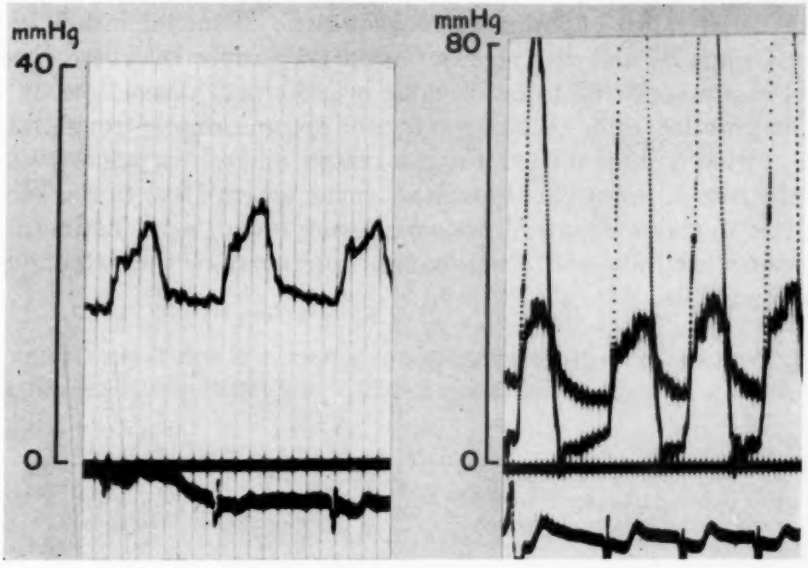

Fig. 1.—Pressure pulses from the patient with pure mitral insufficiency who was operated upon (Group III), as recorded at the time of left heart catheterization (*left*), and during surgery (*right*). Simultaneous left atrial pressure and electrocardiogram, Lead III (*left*); simultaneous left atrial and ventricular pressures and electrocardiogram, Lead II (*right*). Discussed in text. Note that there is no h ascent nor clear evidence of an isotonic trough; also that a marked end-diastolic pressure gradient exists across the mitral valve. Average value for 0.1 Ry/v is 0.32 at catheterization, 0.44 at surgery. Heart rate, average on left, 90 beats/min.; on right, 110/min. Pressure is in mm. Hg.

Allison and Linden,[5] and recently Gunning and Linden,[6] reported excellent results when using the calculation $\frac{v - z}{v} \times 100$, i.e., the difference between the pressure levels of the v and z points expressed as a percentage of v-point pressure. As seen in Fig. 3, this formula effected no clear indication in our series of the nature of the mitral valvular lesion.

***Mean left atrial pressure in Group I (15 observations) ranged from 8 to 43 mm. Hg, with a mean and S.D. of 23.1 ± 9.5 mm. Hg; in Group II (5 observations) the range was 17 to 40 mm. Hg, with a mean and S.D. of 29.4 ± 8.3 mm. Hg. The figures in Group III (6 observations) were 6 to 26 mm. Hg and 15.5 ± 7.7 mm. Hg, respectively. The end-diastolic pressure gradient across the mitral valve in Group I (30 observations) ranged from 6 to 24 mm. Hg, with a mean and S.D. of 13.4 ± 5.0 mm. Hg. The figures in Group II (5 observations) were 10 to 23 mm. Hg and 17.2 ± 4.5 mm. Hg, respectively. While there is considerable overlap, both mean left atrial pressure and end-diastolic gradient across the mitral valve tended to be higher in Group II than in Group I. This might be a reflection of unequal sampling, although the higher figures in Group II are also consistent with exaggerated diastolic mitral valvular flow due to insufficiency coupled with some degree of stenosis.**

Another formula investigated relates v-point pressure to mean pressure (v/m).[7] This was originally applied to the pulmonary arterial wedge pressure pulse. However, good results have been claimed[8,9] when this formula is applied to the left atrial pressure pulse, provided that the mean left atrial pressure exceeds 20 mm. Hg. No differentiation of the character of the mitral valvular lesion was obtained in our series by this calculation (Fig. 4), even when cases in which the left atrial mean pressure was under 20 mm. Hg were excluded.

An apparent isotonic trough in later portions of diastole, presumably characteristic of mitral insufficiency,[10] was not unusual in Group I (Fig. 5), while a definite h ascent, also regarded as characteristic of mitral insufficiency,[11] was absent in Group II, and was rare in Group III (Table I). These observations, therefore, rarely appeared to be of value in individual cases. Also, it was often difficult, in practice, to be certain whether or not an isotonic trough was present, and if so, at what point it started. For this reason, and others (see below), formulae relating the rate of y descent through its entire length (Ry) to the height of the v point,[10] or to mean left atrial pressure,[12] were found to be inapplicable in this series because accurate and consistent measurement of the extent of Ry was so often impossible.

TABLE I. PRESENCE OF AN ISOTONIC TROUGH OF h ASCENT IN THE THREE GROUPS OF CASES

	GROUP I	GROUP II	GROUP III
No h ascent or isotonic trough	30	7	2
Probably or questionable isotonic trough	9	0	4
Definite h ascent	0	0	2

In order to meet these problems, the y descent was used only in its first 0.1 second, since the slope is easily determined during this period and the direct influence of cycle length is eliminated. The Ry/v formula thus modified (0.1 Ry/v) yielded a remarkably good separation of pure mitral insufficiency from significant mitral stenosis with or without associated insufficiency (Fig. 6). The measurement of 0.1 Ry was carried out as previously described.[12] This calculation is simple and the results were easily reproducible, being relatively uninfluenced by respiratory or pulse-rate variations. All but 5 tracings in Group I had values of 0.30 or less; all of the exceptions were cases of associated aortic valvular disease and/or left ventricular failure. Values for 0.1 Ry/v in Group II were mainly in the mitral stenosis range, or fell in the range which was defined arbitrarily by us as borderline (above 0.30 and under 0.40). In Group III, all but one tracing (which was borderline) had values of 0.40 or more, including that of one patient whose left atrial pressure pulse was normal in level and contour (Fig. 7). Results were similar when the first 0.1 second of Ry was related to the mean left atrial pressure[12] (Fig. 8).

Left atrial pressure pulses were obtained in 11 patients both at the time of left heart catheterization and at thoracotomy in the same individual, and were compared in terms of contour and 0.1 Ry/v (Table II). In 8 of the 11 patients

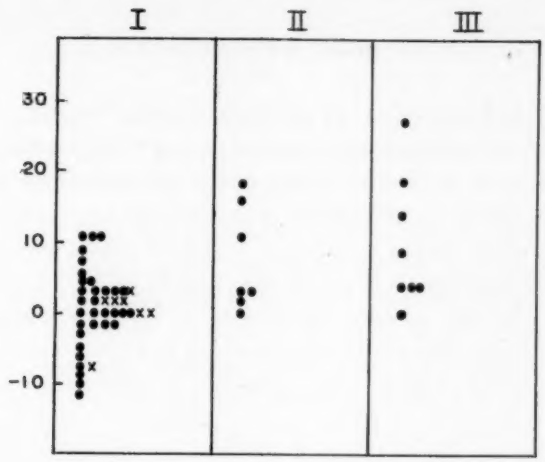

Fig. 2.

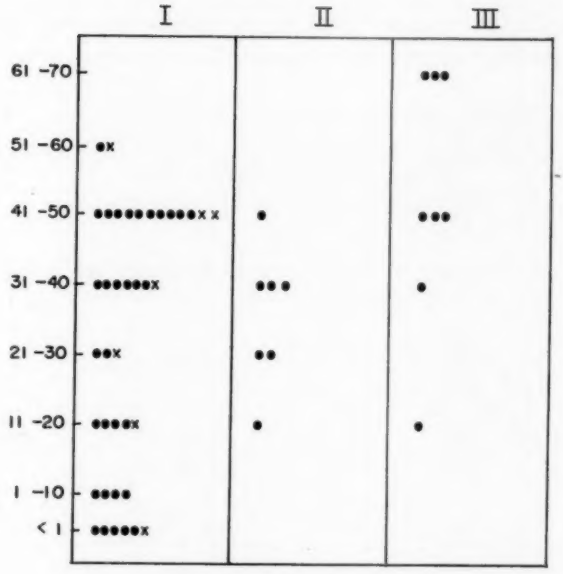

Fig. 3.

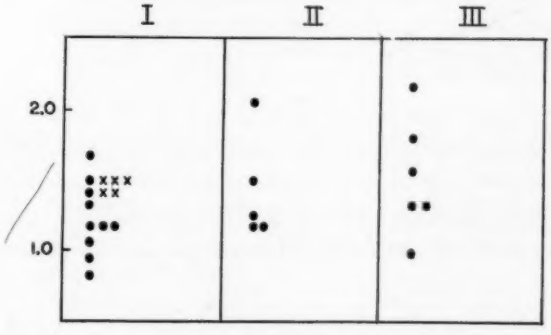

Fig. 4.

Fig. 2.—Values obtained by subtracting pressure at the c point from that at the v point in each left atrial pulse tracing (v-c), in the three groups of cases defined in text. *X* indicates that the tracing was obtained in a patient with aortic valvular disease or left ventricular failure in addition to mitral stenosis. Discussed in text.

Fig. 3.—Values obtained by applying the formula $v - z/v \times 100$ (see text) to left atrial pressure pulses. Conventions as in Fig. 2. Discussed in text.

Fig. 4.—Values obtained by dividing pressure at the v point by mean left atrial pressure (v/m). Conventions as in Fig. 2. Fewer points are present because mean pressure was not determined in all cases. Discussed in text.

(6 in Group I, and 2 in Group II) the formula yielded remarkably similar results under the two sets of circumstances, despite perceptible contour changes in some instances. This similarity was also independent of variations in mean left atrial pressure and in the absolute measurements used in applying the formula. The contour alterations were most evident in cases of sinus rhythm, and took the form of a slight to moderate increase in the height of the v wave relative to the height of the a wave at the time of surgery (Fig. 9). In the remaining 3 patients the value was found to be markedly increased at the time of surgery. One of these patients was in Group I but had aortic stenosis in addition. The other 2 patients fell one each into Groups II and III. The patient from Group III had atrial fibrillation and the two curves appeared grossly similar (Fig. 1). The two tracings from the patient in Group II, on the other hand, looked grossly different (Fig. 10). In these three cases the variation in 0.1 Ry/v under the two conditions was not dependent on the direction of change in mean left atrial pressure, when the latter had altered.

TABLE II. COMPARISON OF 0.1 Ry/v AT LEFT HEART CATHETERIZATION WITH THAT AT THORACOTOMY

GROUP	RHYTHM	VALUE AT LEFT HEART CATHETERIZATION	VALUE AT THORACOTOMY
I	A.F.	0.30	0.30
I	A.F.	0.20	0.16
I	A.F.	0.26	0.24
I	S.R.	0.22	0.23
I	S.R.	0.21	0.24
I	S.R.	0.20	0.25
I*	A.F.	0.25	0.44
II	A.F.	0.17	0.20
II	S.R.	0.34	0.34
II*	S.R.	0.17	0.30
III*	A.F.	0.32	0.44

*The difference in values for 0.1 Ry/v is considered to be significant.
A. F. = Atrial fibrillation. S. R. = Sinus rhythm.

A virtually diagnostic feature of mitral insufficiency in our series, demonstrable during left heart catheterization, was the systolic washout of the catheter from the left ventricle giving rise to pressure pulses of mixed atrial and ventricular form (Fig. 11). This was observed in 4 of the 5 catheterized patients in Group III, in 1 of the 3 similarly studied patients in Group II, and in none of 10 catheterized patients in Group I.

DISCUSSION

The presence of an end-diastolic pressure gradient across the mitral valve is unreliable as a definite indication of pure or predominant mitral stenosis because a considerable pressure gradient may exist at this time in many cases complicated by significant mitral insufficiency, or even in cases of pure mitral insufficiency, as a result of the exaggerated diastolic flow in such states (Fig. 1). Consequently,

much attention has lately been directed to an analysis of some of the features of the left atrial pressure pulse contour as possible aids in determining the nature of the mitral valvular lesion.

The present study revealed that the diastolic portion of the left atrial curve yields the most useful information. Aside from the distensibility characteristics of the system, and other factors (some of which will be discussed below), the pulse contour in diastole, excepting the period of the a wave, depends on momentary differences between the rate of blood inflow into the left atrium and the rate of outflow. This led Owen and Wood[10] to postulate a reduced rate of y descent as an indication of mitral stenosis. The use of a reference pressure level such as the v point (Ry/v) is related to the fact that for a given fall in left atrial volume, Ry will be faster at higher pressure levels (greater distention of the atrium) than at lower levels.

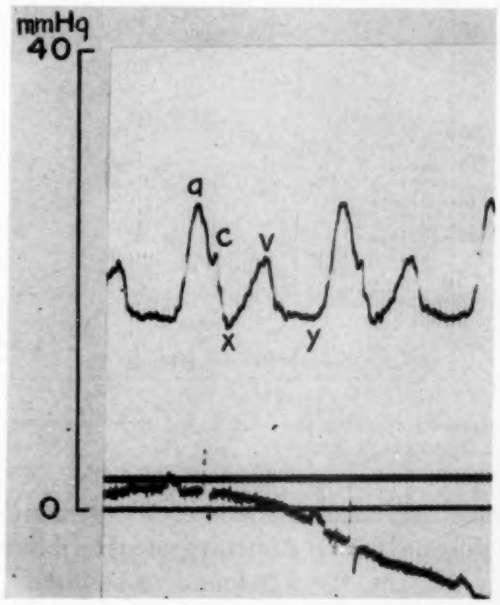

Fig. 5.—Left atrial pressure pulse recorded during suspended breathing at the time of left heart catheterization in a patient with pure tight mitral stenosis (Group I). Average value for 0.1 Ry/v is 0.21. Simultaneous electrocardiogram, Lead I. Heart rate, 67 beats/min. Pressure in mm. Hg. The various features of the left atrial pulse have been labeled. The a wave begins during inscription of P; the c wave is on the downstroke of a and occurs near the summit of R. The v point occurs near the peak or nadir of T. The y point has arbitrarily been placed at the onset of a, but the flatness preceding it makes its location uncertain. Discussed further in text.

In mitral regurgitation, Owen and Wood noted a rapid y descent followed by an isotonic trough, whereas in mitral stenosis the y descent continued through diastole until the next a wave, or in the absence of the latter, until the onset of the c wave. In the present study, there was often great difficulty, even when breathing was arrested, in deciding whether the y descent was followed by an isotonic trough or continued at a reduced rate right up to the onset of the a (or c) wave. This judgment was often a decisive factor as to whether or not Ry/v

suggested mitral stenosis. Another limiting feature in determining the presence of an isotonic trough is diastolic abbreviation when the heart rate is rapid. The presence of an isotonic trough was highly suggestive in 2 of our cases of severe pure mitral stenosis (Fig. 5), and was questionable in 7 other tracings of Group I (Table I). Braunwald and associates[11] have stressed a related phenomenon, the presence of an h ascent in mitral regurgitation. In the present study this feature was absent in Group II even when the heart rate was slow enough so that it might have been expected. Furthermore, an h ascent was present in only 2 of the 8 tracings obtained in Group III.

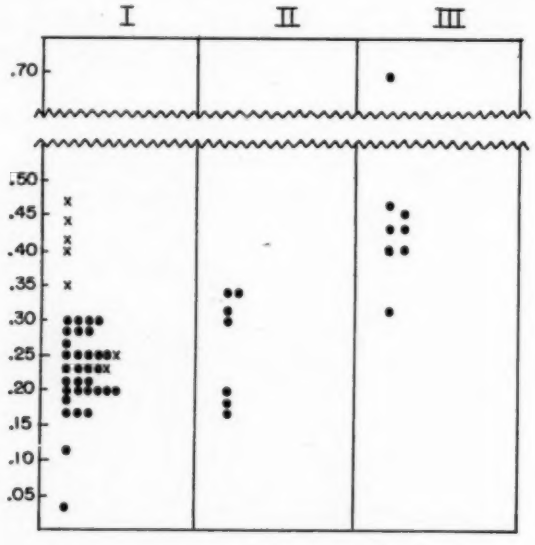

Fig. 6.—Values obtained by applying the formula *0.1 Ry/v* (see text) to left atrial pressure pulses. Conventions as in Fig. 2. Discussed in text.

Calculations based on measurement of Ry presented insurmountable difficulties since, in addition to the difficulty of determining the precise point of termination of the y descent, Ry was found to be highly unstable from cycle to cycle when the heart action was irregular, as in cases of atrial fibrillation. Thus, the Ry/v formula, vulnerable as it is to personal bias, appears to be of little diagnostic value. Because of these problems, it appeared advantageous to utilize only the first part of the y descent, as previously suggested in relating Ry to mean left atrial pressure.[12] The original Ry/v expression of Owen and Wood was modified by utilizing the rate of y descent only during its first 0.1 sec. (0.1 Ry/v). This resulted in good separation of Group III from Groups I and II. There were no false positive values for mitral stenosis in Group III, although one value was borderline. The only borderline or false negative values for mitral stenosis in Group I were in cases with an associated aortic valvular lesion and/or left ventricular failure. The unexpected finding of an elevated 0.1 Ry/v value in such double valvular lesions is unexplained.

It is well known that left atrial pulse form can be affected by aortic valvular disease alone,[13] or by obstruction to left ventricular outflow in the presence of

experimental mitral valve insufficiency.[14] A possible mechanism by which aortic valvular disease might affect 0.1 Ry/v in the presence of mitral stenosis was hinted at by Wells[15] in his evaluation of factors influencing the height of the v wave. The v ascent is usually considered to be an expression of passive atrial filling during ventricular systole, and the y descent as a reflection of mitral valvular flow during early diastole. However, other factors, which may be enhanced by aortic valvular disease, such as the force of contraction of the atrioventricular ring and the pressure on the atrium of the contracting ventricle, might also play a role. Should these factors act to diminish the capacity of the left atrium which has a stenosed outlet, then the height of the v wave would be increased during ventricular systole, and Ry, at least in its early phases, would tend to be more rapid as these effects disappear.

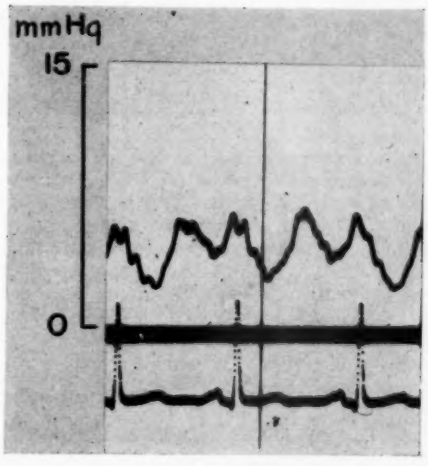

Fig. 7.—Left atrial pressure pulse recorded at the time of left heart catheterization in a patient with the classic manifestations of mitral insufficiency (Group III). Average value for 0.1 Ry/v is 0.43. Simultaneous electrocardiogram, Lead I. Heart rate, 80 beats/min. Pressures in mm. Hg. Discussed in text.

As can be seen by comparing Figs. 6 and 8, the separation of Group III from the other two groups is essentially independent of whether the v point or mean atrial pressure is utilized in relation to 0.1 Ry. Neither formula clearly separates Group II from Group I. This tends to strengthen the view of Owen and Wood that Ry is an expression of the presence or absence of mitral stenosis, but does not of itself indicate whether or not mitral insufficiency is present. Thus, mitral insufficiency is really diagnosed in this way only by the exclusion of mitral stenosis in a patient known to have mitral valvular disease. These observations indicate, however, that marked mitral insufficiency can exist in the presence of mitral stenosis which is sufficiently severe to alter Ry, and they support the concept that significant mitral stenosis and significant mitral insufficiency can coexist. In addition, failure of this formulation to separate Group I from Group II is yet another indication that 0.1 Ry/v depends on factors apart from diastolic mitral valve size. It is to be expected, of course that instances of left ventricular

failure, not necessarily related to mitral insufficiency, such as the case of chronic myocarditis included in Group III of this report, will yield "insufficiency" values, since here too there is no significant obstruction to mitral valvular flow early in diastole. It is conceivable that this might also be a feature of left atrial pressure pulses in normal individuals.

A finding which, when present, is highly suggestive of significant mitral insufficiency is the systolic catheter washout (Fig. 11).[3] This was a prominent feature in Group III, including the one case in which 0.1 Ry/v fell in the borderline range.

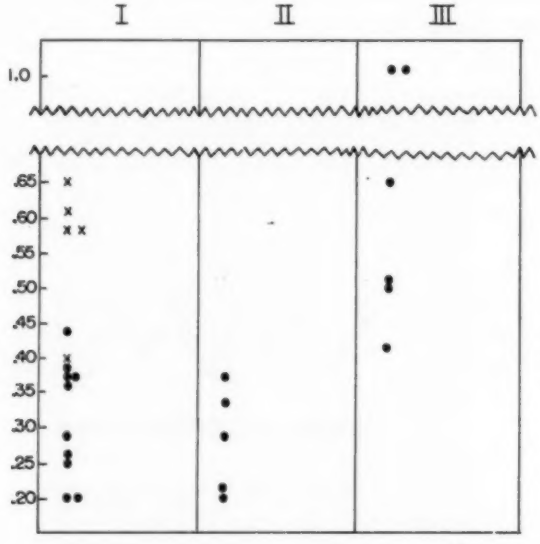

Fig. 8.—Values obtained by applying the formula *0.1 Ry/mean left atrial pressure.* Conventions as in Fig. 2. Although fewer points are present, as in Fig. 4, the results are similar to those shown in Fig. 6. Discussed in text.

In one case of pure mitral insufficiency (Fig. 7) the systolic washout of the catheter was the only abnormal feature of the left heart catheterization. Whereas the value for 0.1 Ry/v was in the "insufficiency" range, the pressure pulse was normal in level and contour, so that it could not of itself be considered diagnostic. Dating from the original experimental studies of Wiggers and Feil[14] on mitral insufficiency, a tall v wave has always been considered a classic alteration of the left atrial pressure pulse induced by mitral insufficiency. It has subsequently been stressed by many that a tall v wave might also occur in mitral stenosis. However, attention should be given to the fact, well exemplified by the patient under consideration, that dynamic mitral insufficiency may be associated with a perfectly normal left atrial pressure pulse. McGregor and Zion[16] cited the occurrence of a normal pulmonary arterial wedge pressure in one case of mitral insufficiency, and others[17] have noted that the pressure pulse was often little altered by significant degrees of experimental mitral insufficiency. Recognition of this fact has led to the suggestion that a pressor amine infusion be made during left heart cathe-

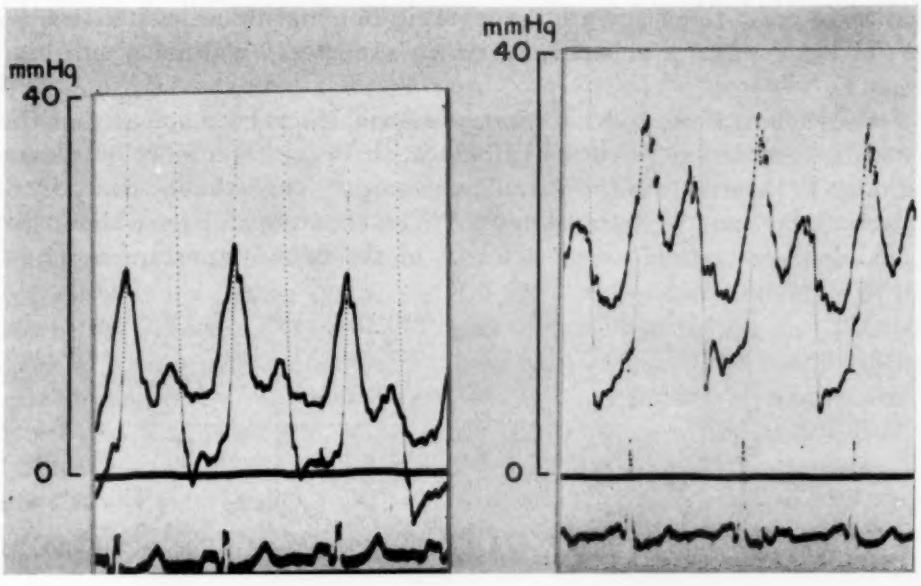

Fig. 9.—Simultaneous left atrial and ventricular pressures recorded at the time of left heart catheterization (*left*), and during surgery (*right*) in a patient with mitral stenosis (Group I). The difference in pressure level between the two tracings may be related in part to differing reference levels, although no systematic difference was evident in the cases studied. Note that the v wave of the left atrial pulse is relatively more prominent at the time of surgery, the contour of the two tracings being otherwise quite similar. Average value for 0.1 Ry/v is 0.20 at catheterization, 0.25 at surgery. Electrocardiogram, Lead I (*left*); Lead II (*right*). Heart rates, 75 and 77 beats/min. Pressures in mm. Hg. Discussed in text.

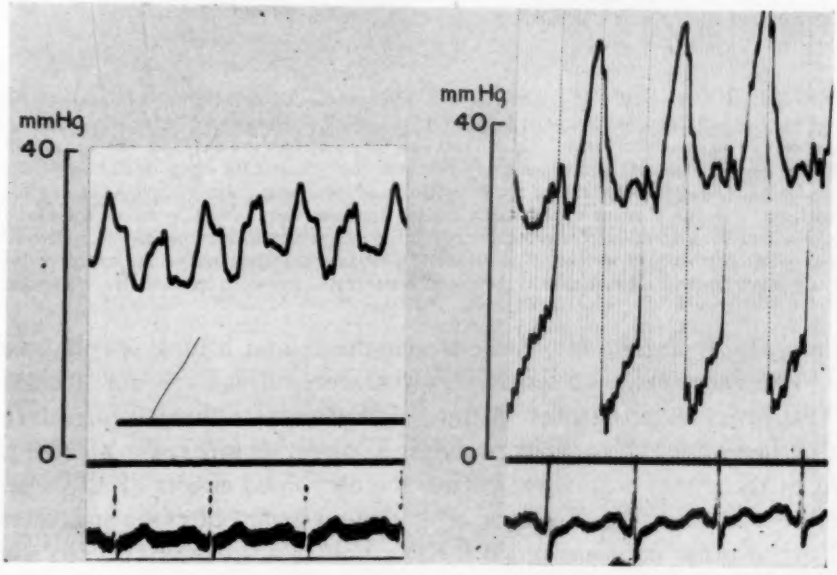

Fig. 10.—Pressure pulses from a patient in Group II, recorded at the time of left heart catheterization (*left*), and during surgery (*right*). Left atrial pressure (*left*); simultaneous left atrial and ventricular pressures (*right*). Electrocardiogram, Lead II. The two left atrial pulses are grossly different in contour. The a wave is relatively smaller and the v wave much taller in the surgical curves. Average value for 0.1 Ry/v is 0.17 at catheterization, 0.30 at surgery. Heart rate, 77 beats/min. (*left*); 88/min. (*right*). Pressure in mm. Hg. Discussed in text.

terization in order to exaggerate the regurgitation and thus elevate the absolute height of the v wave, a phenomenon which supposedly will not occur in mitral stenosis.[18]

From time to time, and for various reasons, it has been stated that the left atrial pulse recorded at left heart catheterization is either a more or a less valid criterion as to the nature of the mitral involvement than is that obtained by direct puncture at the time of thoracotomy.[19,20] The conditions under which pressures are recorded are certainly very different in the two circumstances. Thus, the

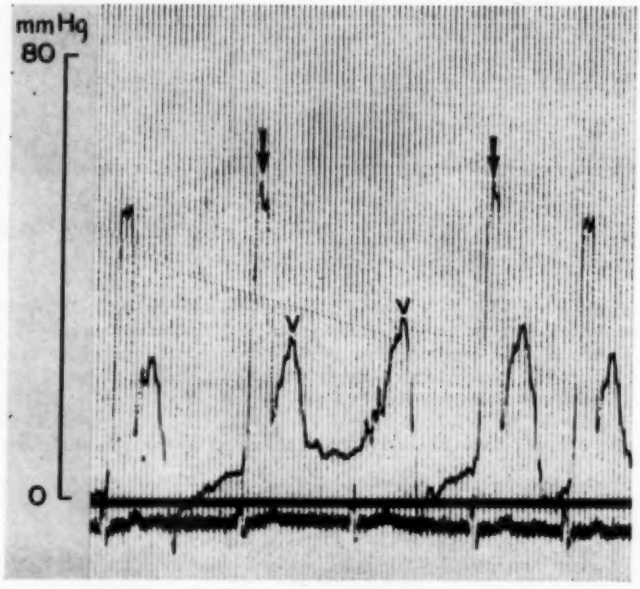

Fig. 11.—Mixed left atrial and ventricular pressure pulse recorded during left heart catheterization of a patient in Group III, illustrating the "catheter washout" phenomenon. With reference to the simultaneously recorded electrocardiogram (Lead I), it can be seen that the catheter enters the left ventricle intermittently during diastole, and is washed back into the left atrium early in the succeeding systole. The arrows indicate interruption of the rise in pressure of left ventricular systole as the catheter washes into the atrium. *V* is the v point of the atrial pulse. Between the labeled v waves the catheter tip remains in the left atrium. In all other cycles it stays in the left ventricle during diastole, and returns to the atrium in systole. Note the presence of a diastolic pressure gradient across the mitral valve. Average value for 0.1 Ry/v is 0.47. Heart rate, average 90 beats/min. Pressure in mm. Hg. Discussed in text.

patient's position is different; there is anesthesia and a lung is collapsed during surgery. The zero reference levels for pressure readings are not necessarily the same. The heart rate, cardiac output, and the systemic peripheral resistance must also be expected to vary widely. A direct comparison of the pressures recorded in these two states, indicating the combined effects of all these factors, is therefore valuable. The findings in this small group of cases suggest: (1) that the left atrial pulse contour and 0.1 Ry/v values are usually grossly similar for practical purposes in the two states, at least in the presence of pure mitral stenosis; (2) that the pulse contour or 0.1 Ry/v may change noticeably between the two states (in this study, all such instances—3 of 11 cases—were associated with mitral insufficiency or aortic valvular disease); (3) that 0.1 Ry/v is less variable than the pulse contour and pressure level.

Instability of left atrial pulse contour and pressure level associated with certain acute changes in state has been demonstrated in experimental animals[14] and in man.[18] The present data indicate that 0.1 Ry/v may also vary under certain circumstances in the same individual, ostensibly without change in diastolic area of the mitral valve. Some of the factors, apart from the presence or absence of mitral stenosis, which may affect 0.1 Ry/v have been mentioned. The data are too scant to permit any conclusion as to which factors are operating in the 3 cases referred to above.

It is concluded that evaluation of the left atrial pressure pulse, as described in this report, is, within certain limitations, well supported by the surgical observations. Thus, careful analysis of the left atrial pressure pulse form merits consideration as part of the total picture in cases in which mitral surgery is contemplated. The catheter washout phenomenon is a valuable sign of significant mitral insufficiency. The rate of y descent in its first 0.1 second provides a useful independent expression of the presence or absence of obstruction to mitral valvular flow in early diastole.

SUMMARY

Fifty-four left atrial pressure pulses from 43 patients, all but one of whom had rheumatic mitral valvular disease, were analyzed for features which might be of aid in distinguishing among "pure" mitral stenosis, "pure" mitral insufficiency, or combined significant lesions. All except 5 patients, who presented as classic cases of mitral insufficiency, underwent surgical exploration of the mitral valve. Thirty-six tracings were recorded at surgery and 18 at left heart catheterization. Eleven sets of tracings were obtained under both circumstances in the same patient. These were subjected to additional analysis.

Although an end-diastolic gradient across the mitral valve was present in all patients with proved mitral stenosis, such a gradient was also found in half of the patients who clinically or at surgery had pure mitral insufficiency. Numerous features of the contour or pressure level of the left atrial pulse effected poor or no separation of the patients in terms of findings at palpation of the valve. Formulae involving the rate of y descent throughout its entire length were inapplicable because of technical difficulties involved in the accurate measurement of this feature.

The most useful feature of the left atrial pulse was the rate of y descent in its initial 0.1 second, related to pressure at the v point (0.1 Ry/v) or to mean left atrial pressure. This resulted in a good separation of patients with mitral stenosis from those without, with the exception of a group of patients with mitral stenosis who had aortic valvular disease in addition. It was found, however, that a degree of mitral stenosis sufficient to significantly slow the rate of the y descent in its initial portion might coexist with a marked degree of mitral insufficiency.

The "catheter washout" phenomenon observed during left heart catheterization was of value. This was present in 5 of 8 patients who had mitral insufficiency, with or without mitral stenosis, and in none of 10 patients with mitral stenosis alone.

In the 11 patients in whom catheterization and surgical curves from the same individual could be compared, 0.1 Ry/v was remarkably constant in 8, despite changes in pressure level, and some alterations in pulse contour.

It is concluded that 0.1 Ry/v is easily determined and is reproducible. Within its limitations, it is worthy of consideration along with the total picture in evaluating patients for mitral valve surgery.

We wish to acknowledge our appreciation for the wholehearted cooperation in this study given by the members of the Cardiac Catheterization Unit and by the thoracic surgeons. We are grateful to Dr. Louis N. Katz, for his advice in preparing the report and to the clinicians who gave us permission to use the data on their patients.

REFERENCES

1. Björk, V. O., Malmström, G., and Uggla, L. G.: Left Auricular Pressure Measurements in Man, Ann. Surg. **138**:718, 1953.
2. Ankeney, J. L., Fishman, A. P., and Fritts, H. W., Jr.: An Analysis of Normal and Abnormal Left Atrial Pressure Pulse in Man, Circulation Res. **4**:95, 1956.
3. Musser, B. G., Bougas, J., and Goldberg, H.: Left Heart Catheterization. II. With Particular Reference to Mitral and Aortic Valvular Disease, Am. Heart J. **52**:567, 1956.
4. Kent, E. M., Ford, W. B., Fisher, D. L., and Childs, T. B.: The Estimation of the Severity of Mitral Regurgitation: A Correlation of Direct Left Atrial Pressure Recordings With Observations Made During Surgical Palpation of the Valve Area, Ann. Surg. **141**:47, 1955.
5. Allison, P. R., and Linden, R. J.: Bronchoscopic Approach for Measuring Pressures in the Left Auricle, Pulmonary Artery and Aorta, Lancet **1**:9, 1955.
6. Gunning, A. J., and Linden, R. J.: Bronchoscopic Method for Measuring Left Atrial Pressure. An Aid in Diagnosis in Mitral Disease, Circulation **17**:354, 1958.
7. Connolly, D. C., and Wood, E. H.: Hemodynamic Data During Rest and Exercise in Patients With Mitral Valvular Disease in Relation to the Differentiation of Stenosis and Insufficiency From the Pulmonary Artery Wedge Pressure Pulse, J. Lab. & Clin. Med. **49**:526, 1957.
8. Fox, I. J., Wakai, C. S., Connolly, D. C., and Wood, E. H.: Left Atrial and Ventricular Pressure Pulses in Mitral Valvular Disease, Proc. Staff Meet. Mayo Clin. **31**:126, 1956.
9. Marshall, H. W., Woodward, E., Jr., and Wood, E. H.: Hemodynamic Methods for Differentiation of Mitral Stenosis and Regurgitation, Am. J. Cardiol. **2**:24, 1958.
10. Owen, S. G., and Wood, P.: A New Method of Determining the Degree or Absence of Mitral Obstruction. An Analysis of the Diastolic Part of Indirect Left Atrial Pressure Tracings, Brit. Heart J. **17**:41, 1955.
11. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M., and Gordon, A. J.: The Hemodynamics of the Left Side of the Heart as Studied by Simultaneous Left Atrial, Left Ventricular, and Aortic Pressures: Particular Reference to Mitral Stenosis, Circulation **12**:69, 1955.
12. Morrow, A. G., Braunwald, E., Haller, J. A., Jr., and Sharp, E. H.: Left Heart Catheterization by the Transbronchial Route: Technique and Applications in Physiologic and Diagnostic Investigations, Circulation **16**:1033, 1957.
13. Gorlin, R., McMillan, I. K. R., Medd, W. E., Mathews, M. B., and Daley, R.: Dynamics of the Circulation in Aortic Valvular Disease, Am. J. Med. **18**:855, 1955.
14. Wiggers, C. J., and Feil, H.: Cardiodynamics of Mitral Insufficiency, Heart **9**:149, 1922.
15. Wells, B. G.: The Diagnosis of Mitral Incompetence From Left Atrial Pressure Curves, Brit. Heart J. **20**:321, 1958.
16. McGregor, M., and Zion, M. M.: The Diagnosis of Mitral Incompetence in the Presence of Mitral Stenosis, Acta med. scandinav., Suppl. 306:111, 1955.
17. Wilder, R. J., Moscovitz, H. L., and Ravitch, M. M.: Transventricular and Aortic Angiocardiography and Physiologic Studies in Dogs With Experimental Mitral and Aortic Insufficiency, Surgery **40**:86, 1956.
18. Braunwald, E., Welch, G. H., Jr., and Morrow, A. G.: The Effects of Acutely Increased Systemic Resistance on the Left Atrial Pressure Pulse: A Method for the Clinical Detection of Mitral Insufficiency, J. Clin. Invest. **37**:35, 1958.
19. Fisher, D. L.: The Use of Pressure Recordings Obtained at Transthoracic Left Heart Catheterization in the Diagnosis of Valvular Heart Disease, J. Thoracic Surg. **30**:379, 1955.
20. Rubin, M., and Shah, S.: The Transbronchial Measurement of Left Atrial Pressures in Mitral Stenosis and Insufficiency, Am. Heart J. **55**:55, 1958.

Electrocardiographic Changes in Atrial Septal Defects: Ostium Secundum Defect Versus Ostium Primum (Endocardial Cushion) Defect

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Today, open-heart surgery is being performed at many centers throughout the world, but the number of pump-oxygenators and pump teams is still somewhat limited. Thus, it is of paramount importance that the cardiologist be able to distinguish the secundum type of atrial septal defect from the ostium primum (endocardial cushion) type of atrial septal defect, for the ostium secundum type of defect may be closed under hypothermia but the ostium primum type of defect should be repaired with the aid of the pump-oxygenator.

Many authors[1-8] have described the electrocardiographic changes in the secundum type of atrial septal defect; several investigators[4,8-11] have reported the electrocardiographic changes in the ostium primum type of defect; and a few authors[4,8,12,13] have compared the electrocardiographic changes in the two types of defects.

It is the purpose of this paper to describe the electrocardiographic changes in atrial septal defects and to compare the electrocardiographic changes in the ostium secundum type of defect with those in the ostium primum or endocardial cushion type of defect. This communication will emphasize that the electrocardiogram is a valuable tool in the diagnosis of the secundum type of atrial septal defect, and will propose that the electrocardiogram is of cardinal importance in the differentiation of the ostium primum or endocardial cushion defect from the secundum type of defect.

Vectorial analysis of the standard (14-lead) electrocardiogram is considered by the authors to be the most fundamental and useful method of electrocardiographic interpretation.

METHODS AND MATERIALS

One hundred thirty-three patients were studied. One hundred patients had surgically proved secundum type of atrial septal defect. Thirty-three patients were diagnosed as having the ostium

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primum type of atrial septal defect. Sixteen (48.5 per cent) of the 33 instances of the ostium primum type of defect were proved at operation and/or autopsy. Twenty-three of the patients with an ostium primum type of defect underwent cardiac catheterization. It is considered that true left axis deviation, mitral insufficiency, left ventricular hypertrophy, an accompanying ventricular septal defect, or any combination of these criteria, are all incompatible with a diagnosis of a straightforward secundum type of atrial septal defect. In the patients with an ostium primum type of atrial septal defect, true left axis deviation was present in 82 per cent, mitral insufficiency in 79 per cent, left ventricular hypertrophy in 57 per cent, and a ventricular septal defect in 33 per cent.

Table I shows the age and sex distribution, and the number of Mongolians in the two groups. Standard (14-lead) electrocardiograms were obtained on all patients, and the electrocardiograms were analyzed by the spatial vector approach as described by Grant.[14]

TABLE I. AGE AND SEX DISTRIBUTION OF THE 100 PATIENTS WITH OSTIUM SECUNDUM AND 33 PATIENTS WITH OSTIUM PRIMUM TYPE OF ATRIAL SEPTAL DEFECT

	100 PATIENTS WITH SECUNDUM TYPE OF A. S. D.	33 PATIENTS WITH OSTIUM PRIMUM TYPE OF A. S. D.
Age: 0–10	33	16
10–20	25	13
20–30	24	2
30–40	13	0
40–50	5	1
50–60	0	1
Sex: Female	68	13
Male	32	20
Mongolians	0	4
Mentally Deficient	0	2

RESULTS AND DISCUSSION

Analysis of the Preoperative Electrocardiograms.—

Rhythm: All 133 patients had a normal sinus rhythm preoperatively. Wood[4] observed atrial fibrillation in 10 per cent of the patients with the secundum type of atrial septal defect, but noted that this arrhythmia was related to age and occurred in the older patients. Milnor and Bertrand[12] found atrial fibrillation in 3 of 24 patients (6 with ostium primum and 18 with ostium secundum defects). They also noted that the arrhythmia occurred in the older patients. The patients in our series fall mainly into the younger age groups, so that the lack of arrhythmias is not unexpected.

P Waves: The height of the P wave in Lead II and/or Lead V_2 exceeded 2.5 mm. in 25 per cent of the ostium secundum patients and in 18 per cent of the ostium primum patients. Analysis of the ratio of the P-wave duration to the P-R segment duration failed to increase the accuracy of the diagnosis of right atrial enlargement. Kjellberg and associates[8] found abnormally tall P waves in Lead V_1 in 30 per cent of ostium secundum patients. Wood[4] observed the P waves to be normal in height in 90 per cent of the patients with ostium secundum type of atrial defect. Sodi-Pallares and Marsico[5] reported abnormal P waves in 38 per cent of patients having atrial septal defects. Since the right atrium is always

enlarged in patients with atrial septal defects, it was somewhat unexpected that more patients did not show electrocardiographic signs of right atrial enlargement. No correlation was found between the height of the P waves and the pulmonary arterial pressure. Analysis of the mean P vector and measurement of the width of the P wave were not found to be helpful in this study.

P-R Interval: The P-R interval measured more than 0.20 second in 6 per cent of the secundum defects and in 18 per cent of the ostium primum defects. Walker and associates[7] found P-R prolongation in 6.3 per cent of the 95 secundum type of atrial septal defects studied. Other authors[4,5,8,14] report an incidence of P-R prolongation varying from 10 to 26 per cent. De Oliveira and Zimmerman[6] observed that a prolonged P-R interval occurred only with large left-to-right shunts. Milnor and Bertrand[12] found the incidence of P-R prolongation to be higher in ostium primum than in ostium secundum defects.

QRS Width: The QRS duration measured 0.10 second or less in 91 per cent of the secundum defects and in 76 per cent of the ostium primum defects. A QRS width of 0.11 second was found in 4 per cent of the secundum defects and in 9 per cent of the ostium primum defects. "Complete" right bundle branch block with a QRS duration of 0.12 second or more was present in 5 per cent of the secundum defects and in 15 per cent of the ostium primum defects. Many authors have reported QRS durations in terms of "incomplete" or "complete" right bundle branch block. Milnor and Bertrand[12] and Walker and associates[7] found similar incidences of the aforementioned divisions of QRS width.

Table II summarizes the observations on the P wave, P-R interval, and QRS width described above.

TABLE II. SUMMARY OF OBSERVATIONS ON THE P WAVE, P-R INTERVAL, AND QRS WIDTH IN THE SECUNDUM AND PRIMUM GROUPS

	SECUNDUM TYPE A. S. D. (% OF 100 PATIENTS)	OSTIUM PRIMUM TYPE A. S. D. (% OF 33 PATIENTS)
"P" wave >2.5 mm. in Lead II and/or Lead V_2	25	18
P-R interval >0.20 sec.	6	18
QRS width:		
0.10 sec. or less	91	76
0.11 sec.	4	9
0.12 sec. or more (RBBB)	5	15

QRS Vectors.—All electrocardiograms were analyzed by the vector method, and the frontal plane "mean QRS vector," "mean initial (0.04 second) vector," and "terminal vector" were plotted on the triaxial reference figure for each patient. The findings are presented below.

Mean QRS Vector: Right axis deviation (more than +100° rightward) was found in 81 per cent of the ostium secundum defects and in none of the ostium primum defects. When "complete" right bundle branch block was present, then only the first 0.07 to 0.08 second of the QRS was used to determine the mean QRS axis. The mean QRS vector fell between +50° and 180° on the triaxial

reference figure in all 100 cases of the secundum type of atrial septal defect. Thus, none of the secundum defects showed left axis deviation.

"True" left axis deviation (more than −30° leftward) was found in 82 per cent of the cases of ostium primum type of atrial septal defect. Nine per cent of the ostium primum defects had a 0° axis, and 9 per cent fell between +10 and +95°. None of the ostium primum defects showed true right axis deviation.

Table III summarizes the above findings, and Fig. 1 shows the mean QRS vector for each of the 133 patients plotted on the triaxial reference figure.

TABLE III. SUMMARY OF FINDINGS ON THE MEAN QRS AXIS IN THE SECUNDUM AND PRIMUM GROUPS

MEAN QRS AXIS	100 PATIENTS WITH SECUNDUM TYPE OF A. S. D.	33 PATIENTS WITH OSTIUM PRIMUM TYPE OF A. S. D.
True right axis deviation (> +100° rightward)	81%	0
True left axis deviation (> −30° leftward)	0	82%
0° axis	0	9%
+10° to +90°	19%	9%

Grant[14] found an incidence of 80 per cent right axis deviation in secundum defects, and 50 per cent left axis deviation in primum defects. Milnor and Bertrand[12] found a 50 per cent incidence of left axis deviation in ostium primum defects. Sodi-Pallares and Marsico[5] found the QRS axis to fall between +90° and +170° in all but one of 50 cases of atrial septal defect. Kiely and associates[10] found left axis deviation in 10 of 14 patients with ostium primum defect. J. M. Martt, M.D. (University of Missouri Medical Center) has recently gathered data on ostium primum defects from eight medical centers (including our own) and the literature. One hundred thirty-one of the 146 patients diagnosed as having ostium primum defects had left axis deviation.

It is considered that mitral insufficiency and/or a ventricular septal defect accounts for the left ventricular hypertrophy that may be revealed by electrocardiography or fluoroscopy, but the authors do not believe that the left ventricular hypertrophy per se is the cause of the left axis deviation. The left axis deviation found in these endocardial cushion defects is probably due to an alteration of excitation pathways rather than to left ventricular hypertrophy.

At this time it is important to point out that the QRS vector loop, when plotted from the limb leads and projected on the frontal plane, rotated counterclockwise in all of our 27 patients with true left axis deviation. This loop is superior to the "isoelectric line" (0-180°) and sometimes has a flat figure-of-eight configuration. This important feature of the QRS loop was first emphasized by Toscano-Barbosa, Brandenburg and Burchell[11] in their analysis of 16 patients with endocardial cushion defects. They pointed out that the basic electrocardiographic pattern of ostium primum defects may be modified by pulmonary hypertension or gross left ventricular hypertrophy due to mitral insufficiency.

The QRS vector loop, projected on the frontal plane, rotated clockwise and was below the isoelectric line (0-180°) in all 100 patients with the secundum type

of defect. Fig. 2 shows a typical QRS vector loop, projected on the frontal plane, from the electrocardiogram of a patient with a secundum defect and from the electrocardiogram of a patient with an ostium primum defect.

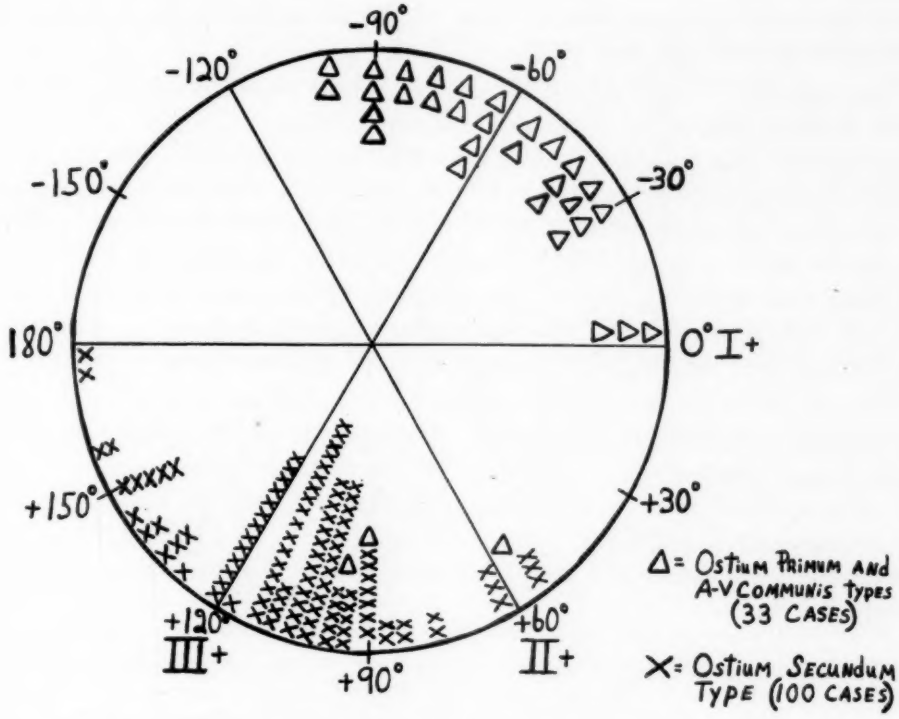

Fig. 1.—Mean QRS vector (axis) of each patient plotted on the triaxial reference figure.

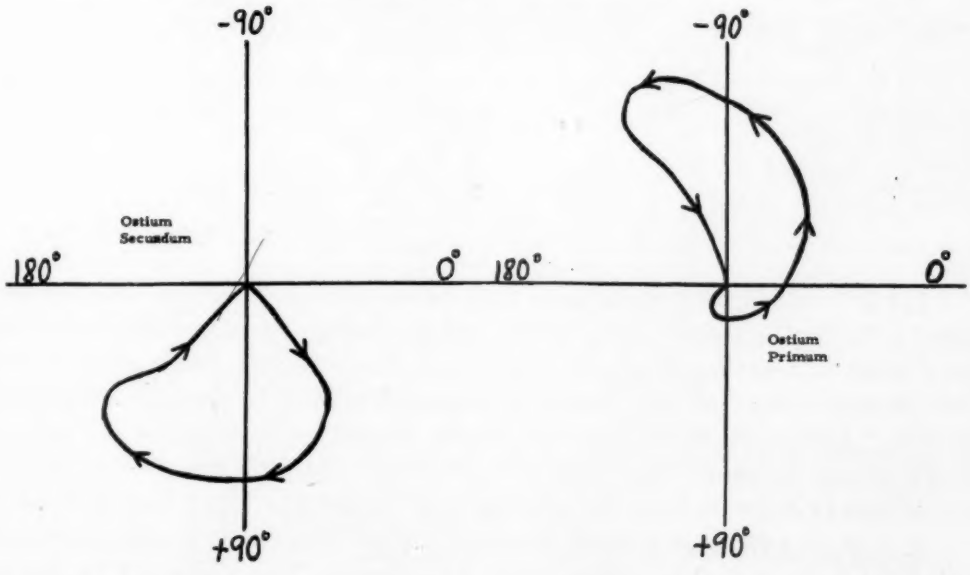

Fig. 2.—Comparison of the QRS vector loops, plotted from the limb leads and projected on the frontal plane, in the ostium secundum and in the ostium primum defects.

Initial (0.04 Second) QRS Vector: Fig. 3 shows the distribution of the initial vectors for all 133 patients when plotted on the triaxial reference figure. All of these initial vectors fall in a normal range (−25° to +90°), but it can be seen that there is a definite tendency for the initial vectors for the ostium primum group to be more leftward. Twenty-four of the 33 ostium primum initial QRS vectors fell between −25° and +10°.

Terminal QRS Vector: Fig. 4 shows the frontal plane terminal QRS vector for each patient plotted on the triaxial reference figure. It can be seen that this terminal vector falls between +120° and −150° in the majority (91 per cent) of the cases of secundum defect, and between −60° and −140° in 91 per cent of the cases of ostium primum defect. The terminal QRS vector is a very influential force, for it plays a major role in determining the direction of the important mean QRS axis described above. The terminal QRS vector is usually directed rightward and anteriorly, and this accounts for the R′ in Lead V_1, which is one of the hallmarks of the electrocardiogram in atrial septal defects.

Type of QRS Complex in Lead V_{3R} or Lead V_1.—There are six types of QRS complexes seen in precordial leads V_{3R} or V_1 in all atrial septal defects, both secundum and primum types. Examples of the rSr′ (crista) pattern, rSR′ (right ventricular outflow tract hypertrophy) pattern, rR′ pattern, and qR pattern (right ventricular hypertrophy) are shown in Fig. 5, and the incidence of the various patterns is shown in Table IV. A description and discussion of each type of complex follows.

TABLE IV. TYPE OF QRS COMPLEX IN LEAD V_{3R} OR LEAD V_1, AND OCCURRENCE OF EACH, IN THE SECUNDUM AND THE PRIMUM GROUPS

TYPE OF QRS IN LEAD V_{3R} OR LEAD V_1	OCCURRENCE IN 100 PATIENTS WITH SECUNDUM TYPE OF A. S. D. (%)	OCCURRENCE IN 33 PATIENTS WITH OSTIUM PRIMUM TYPE OF A. S. D. (%)
rsR′ (RVOH)	65	44
Rs or qR (RVH)	23	28
RBBB ("Complete")	5	15
rS (Normal)	0	6.5
rSr′ ("Crista")	7	6.5

1. *rSr′* with a QRS duration of 0.11 second or less:* This type of complex is called a "crista" pattern and is within normal limits. In this pattern the r and the r′ must be less than 5 mm. in height and of less magnitude than the S wave. Late depolarization of the "crista supraventricularis" is probably responsible for the r′ deflection. Seven per cent of the secundum defects and 6.5 per cent of the ostium primum defects showed a "crista" pattern. Also, 6.5 per cent of the ostium primum defects had a normal rS pattern in Lead V_{3R} or Lead V_1.

2. *rsR′ or rSR′ with a QRS duration of 0.11 second or less:* This pattern is called "right ventricular outflow tract hypertrophy," as described by Blount,

*Lower and upper case letters indicate small or large deflections, respectively, of an R, S, or R′.

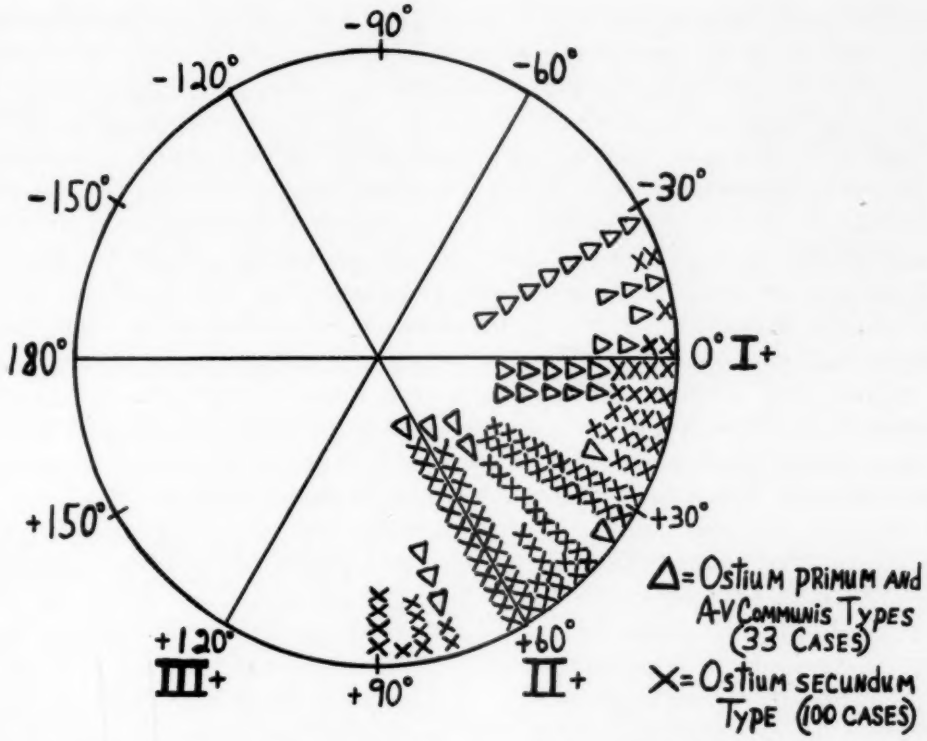

Fig. 3.—Initial (0.04 second) QRS vector of each patient plotted on the triaxial reference figure.

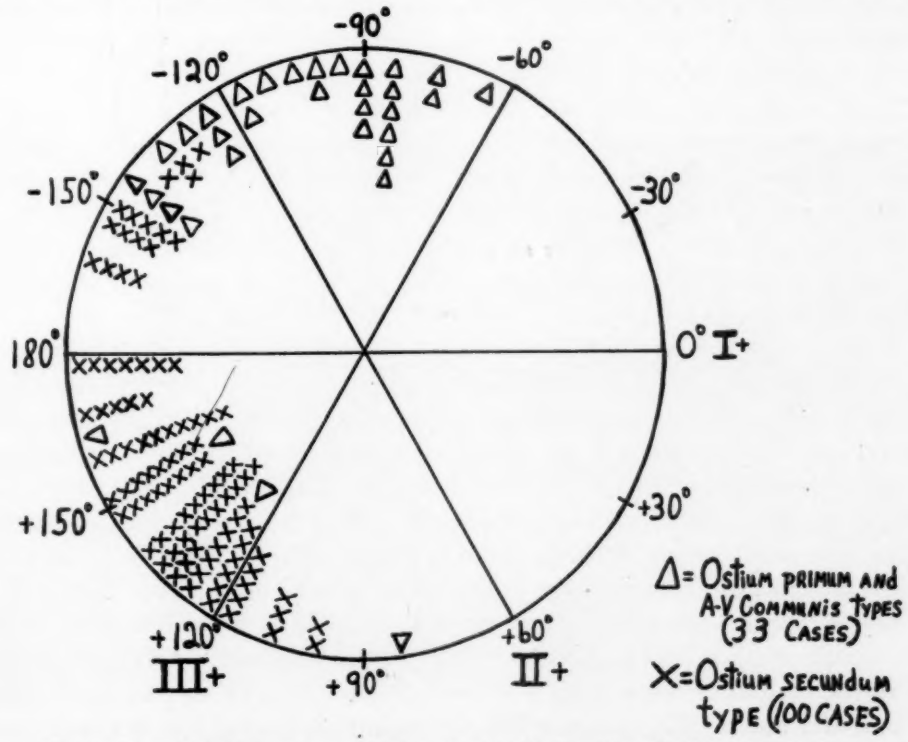

Fig. 4.—Terminal QRS vector of each patient plotted on the triaxial reference figure.

Munyan, and Hoffman.[15] In this type of QRS complex the R′ should be more than 5 mm. in height and of greater magnitude than the S wave. The average height of the R′ wave in this series was 10.5 mm. Sixty-five per cent of the secundum defects and 44 per cent of the ostium primum defects showed this type of QRS complex in Lead V_{3R} or Lead V_1. The name applied to this type of QRS complex is largely a problem of semantics; it is more important to attempt to understand the cause of the pattern. Recent studies reveal that "incomplete right bundle branch block," as this pattern is often called, is probably a relatively uncommon and unlikely cause of this type of QRS complex. Thus, it is unlikely that the rsR′ pattern is due to any real interruption of conduction in the right bundle branch. Cabrera and Monroy[16] pointed out the electrocardiographic changes of systolic and diastolic overloading of the heart. Ventricular enlargement, whether due to hypertrophy or to dilatation, may produce the same QRS changes; however, dilatation is more often accompanied by minor conduction defects than is hypertrophy. When ventricular enlargement is due to increased flow, then this is called diastolic overloading. Right ventricular diastolic overloading is usually characterized by slight QRS prolongation and a prominent R′ deflection in Lead V_{3R} or Lead V_1. Systolic overloading of the right ventricle is usually characterized by a tall R in Lead V_1, with no QRS prolongation (i.e., Rs or qR). At our present state of knowledge it is probably best to think of the rSR′ pattern as being due to dilatation of the right ventricle, and especially to dilatation and/or hypertrophy of the region of the outflow tract of the right ventricle. It must be noted that the rSR′ pattern is not confined to patients with right ventricular diastolic overloading, for it may be seen in those with pulmonary stenosis, cor pulmonale, and mitral stenosis, but it is much more common in patients with diastolic overloading or right ventricular dilatation.

3. *rR′ pattern with QRS time of 0.11 second or less:* In this type of complex there is a notch on the upstroke of the R wave, as if an attempted S failed to reach the base line. This pattern probably falls between the rSR′ and Rs patterns but will be put with the Rs group when percentage of occurrence is quoted.

4. *Rs pattern with a QRS duration of 0.11 second or less:* In this type of complex the R wave is 0.04 second wide, more than 5 mm. tall, and is of greater magnitude than the s wave.

5. *qR pattern with a QRS duration of 0.11 second or less:* The R wave of this pattern is more than 5 mm. tall. Twenty-three per cent of the secundum defects and 28 per cent of the ostium primum defects showed an rR′, Rs, or qR in Lead V_{3R} or Lead V_1. The Rs and qR patterns were seen a little more frequently in the older patients and in patients with higher than usual pulmonary arterial pressures or total pulmonary resistances, but this observation was by no means uniform or predictable. This pattern denotes right ventricular hypertrophy. The average height of the R wave in this group was 12 mm.

6. *rsR′ pattern with a QRS duration of 0.12 second or more:* This is "complete" right bundle branch block. Five per cent of the secundum defects and 15 per cent of the ostium primum defects showed this pattern. It may again be pointed out that the mean QRS axis may be determined by using the first 0.06 to 0.07 second of the QRS complex in order to plot this important mean QRS vector.

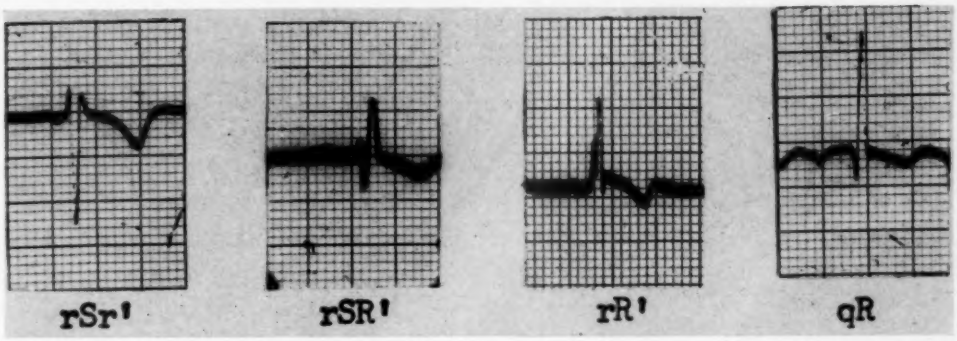

Fig. 5.—An example of four types of QRS complexes that may be seen in Lead V_{3R} or Lead V_1 in atrial septal defects.

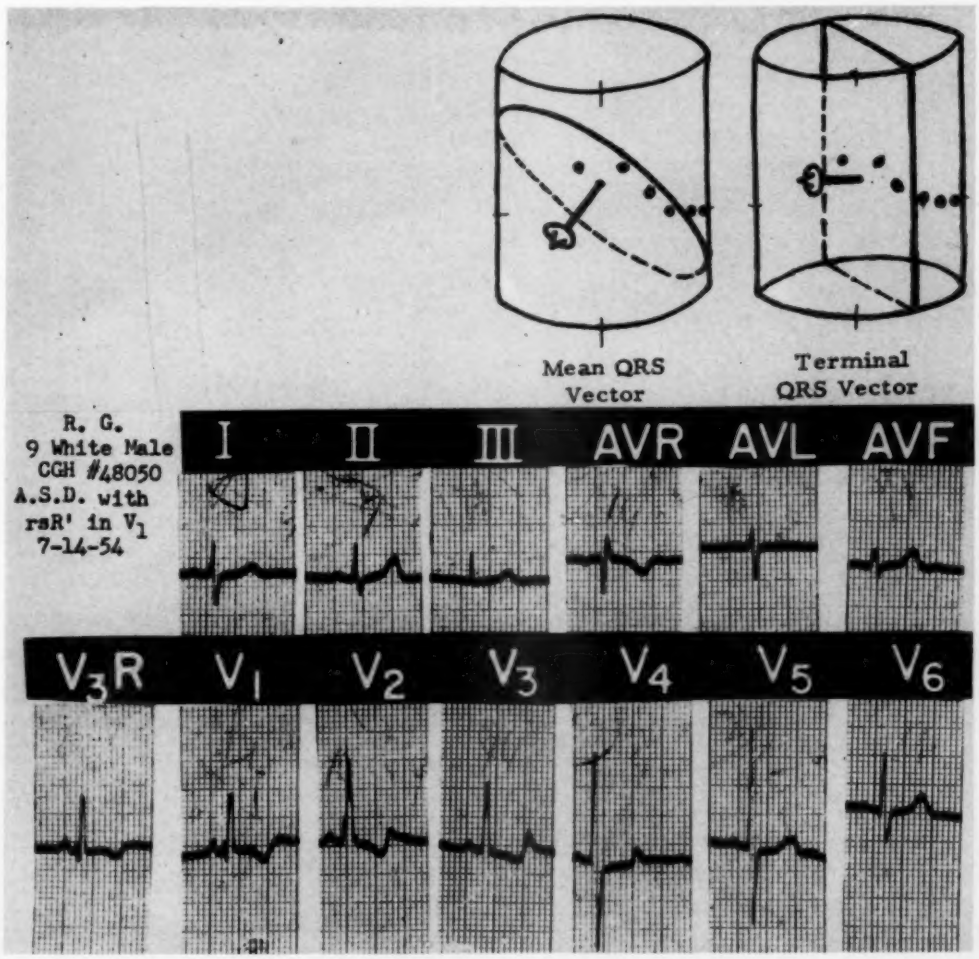

Fig. 6.—A typical ECG of a patient with an ostium secundum type of atrial septal defect, with the mean and terminal QRS vectors plotted.

If the R′ wave in "complete" right bundle branch block is more than 15 mm. in height, then right ventricular hypertrophy may also be suspected.

Demonstration of Electrocardiograms.—Fig. 6 shows the electrocardiogram of a typical ostium secundum type of atrial septal defect. The mean QRS vector is +125° (right axis deviation) and anteriorly directed. The vector loop for the QRS complex is clockwise and below the isoelectric (0-180°) line. The terminal QRS vector is 180° and anteriorly directed. There is an rsR′ in Lead V_1.

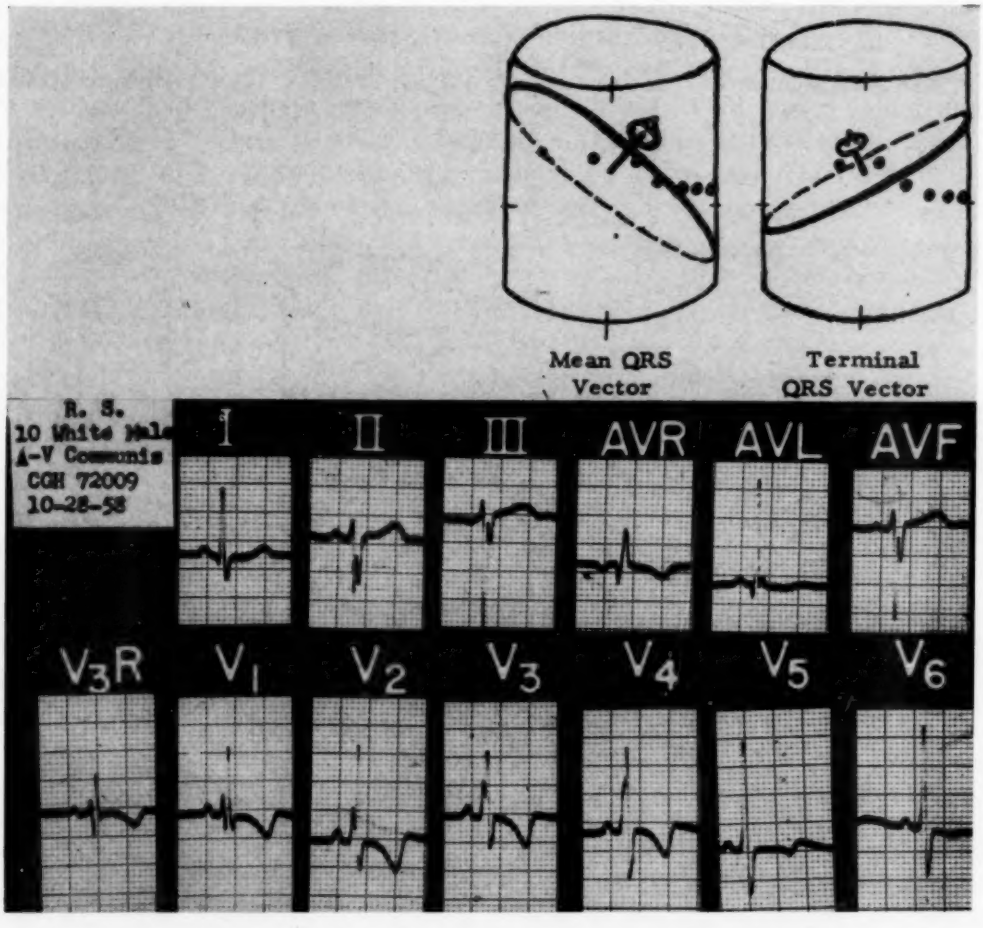

Fig. 7.—A typical ECG of a patient with an ostium primum type of atrial septal defect, with the mean and terminal QRS vectors plotted.

Fig. 7 shows the electrocardiogram of a typical ostium primum type of atrial septal defect. The mean QRS vector is −55° (true left axis deviation) and posteriorly directed. The terminal QRS vector is −105° and anteriorly directed. The QRS loop is counterclockwise and is above the isoelectric line (0-180°). There is an rsR′ in Lead V_1.

Attempted Hemodynamic Correlation.—No useful correlation was found between the pulmonary arterial pressure and the mean QRS axis, the total pulmo-

nary resistance and the mean QRS axis, pulmonary flow and the mean QRS axis, the height of the R′ in Lead V_1 and the pulmonary arterial pressure, the height of the R′ in Lead V_1 and the total pulmonary resistance, and the height of the R′ in Lead V_1 and the pulmonary flow.

Postoperative Results in the Secundum Defects.—The R′ in Lead V_1 may actually increase in height shortly after surgery, but it then starts to decrease in magnitude within approximately 2 months, and usually a definite decrease in height of this R′ deflection is noted within 4 months after the secundum type of atrial septal defect has been closed. This decrease in the height of the R′ in Lead V_1 is usually rapid during the first 6 months after surgery, but then the rate of decrease tapers off, although continued regression may take place for 5 years. Most frequently, the rsR′ pattern of hypertrophy of the right ventricular outflow track regresses to a normal rSr′.

It has been observed almost uniformly that if the R′ does not decrease in size following surgery, then the atrial septal defect is still open. Our experience with postoperative follow-up of ostium primum defects is still too limited to allow comment on the electrocardiographic changes. So far, it has been observed that the R′ in Lead V_1 decreases in height but the left axis deviation persists.

SUMMARY

The electrocardiographic changes in 100 patients with ostium secundum type, and 33 patients with ostium primum type, of atrial septal defect have been described, and the difference between the electrocardiograms of these two groups has been emphasized.

The most reliable single electrocardiographic change that has been found to be of greatest diagnostic value in all atrial septal defects is the presence of an rsR′ (with a QRS duration of less than 0.11 second) in Lead V_1. This pattern was present in 65 per cent of the secundum defects and 44 per cent of the ostium primum defects. The R′ is a manifestation of the rightward and anteriorly directed terminal QRS vector. We call this rsR′ pattern "right ventricular outflow tract hypertrophy" and believe that it is actually due to right ventricular dilatation, especially dilatation and/or hypertrophy in the region of the right ventricular outflow tract, rather than to any interruption of conduction in the right bundle branch.

An Rs or qR pattern in Lead V_1 was present in 23 per cent of the secundum and 28 per cent of the ostium primum defects.

"Complete" right bundle branch block was present in 5 per cent of the patients with secundum, and 15 per cent of the patients with ostium primum, defects.

The mean QRS axis and the rotation of the QRS vector loop are of cardinal importance in differentiating the secundum from the primum defect. True right axis deviation (mean QRS axis or vector more than +100° rightward) was present in 81 per cent of the secundum defects and in none of the primum defects. The mean QRS axis fell between +50° and 180° in all 100 cases of secundum defect. The QRS vector loop was clockwise and below the isoelectric line (0-180°) in all 100 cases of secundum defect.

Left axis deviation (mean QRS axis or vector more leftward than $-30°$) was present in 82 per cent of the ostium primum defects and in none of the secundum defects. The mean QRS axis fell between 0° and $-100°$ in 90 per cent of the primum defects. The QRS vector loop rotated counterclockwise and was above the isoelectric line (0-180°) in all 27 of the patients with ostium primum defect who had true left axis deviation.

The terminal QRS vector fell between $+120°$ and $-150°$ in 91 per cent of the secundum defects, and between $-60°$ and $-140°$ in 91 per cent of the ostium primum defects.

The height of the P waves suggested right atrial enlargement in 25 per cent of the secundum defects and in 18 per cent of the primum defects.

The P-R interval was prolonged in 6 per cent of the secundum and 18 per cent of the primum defects.

Attempted hemodynamic correlation with the electrocardiogram failed to add any useful information to this study or to studies already described by other authors.[6,7,11,12]

Following surgical closure of the secundum defect the R′ begins to decrease within 2 months, and usually decreases significantly within 4 months. There is often a normal rSr′ or rS in Lead V_1 within 1 year after closure. If regression does not occur, then there is cause for doubt as to the complete closure of the defect, or the presence of irreversible pulmonary vascular changes may be suspected.

REFERENCES

1. Bedford, E., Papp, C., and Parkinson, J.: Atrial Septal Defect, Brit. Heart J. **3**:37, 1941.
2. Barber, J. M., Magidson, E., and Wood, P.: Atrial Septal Defect, With Special Reference to the Electrocardiogram, the Pulmonary Artery Pressure, and the Second Heart Sound, Brit. Heart J. **12**:277, 1950.
3. Smull, N. W., and Lamb, L. E.: Interauricular Septal Defect; Correlation of Clinical, Radiologic, and Electrocardiographic Findings in 15 Cases, With Special Reference Given to the Electrocardiogram, Am. Heart J. **43**:481, 1952.
4. Wood, P.: Diseases of the Heart and Circulation, Ed. 2, Philadelphia, 1957, J. B. Lippincott Company.
5. Sodi-Pallares, D., and Marsico, F.: The Importance of Electrocardiographic Patterns in Congenital Heart Disease, Am. Heart J. **49**:202, 1955.
6. De Oliveira, J. M., and Zimmerman, H. A.: The Electrocardiogram in Interatrial Septal Defects and Its Correlation With Hemodynamics, Am. Heart J. **55**:369, 1958.
7. Walker, W. J., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H.: Electrocardiographic and Hemodynamic Correlation in Atrial Septal Defect, Am. Heart J. **52**:547, 1956.
8. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, Year Book Publishers, Inc.
9. Blount, S. G., Jr., Balchum, O. J., and Gensini, G.: Persistent Ostium Primum Atrial Septal Defect, Circulation **13**:499, 1956.
10. Kiely, B., Adams, P., Jr., Anderson, R. C., and Lester, R. G.: The Ostium Primum Syndrome, A.M.A.J. Dis. Child. **96**:381, 1958.
11. Toscano-Barbosa, E., Brandenburg, R. O., and Burchell, H. B.: Electrocardiographic Studies of Cases With Intracardiac Malformations of the Atrioventricular Canal, Proc. Staff. Meet. Mayo Clin. **31**:513, 1956.
12. Milnor, W. R., and Bertrand, C. A.: The Electrocardiogram in Atrial Septal Defect, Am. J. Med. **22**:223, 1957.
13. Sawyer, C. G., Johnston, F. R., Rogers, J. W., and Meredith, J. H.: Atrial Septal Defects, South. M. J. **51**:704, 1958.
14. Grant, R. P.: Clinical Electrocardiography, New York, 1957, McGraw-Hill Book Company.
15. Blount, S. G., Jr., Munyan, E. A., Jr., and Hoffman, M. S.: Hypertrophy of the Right Ventricular Outflow Tract, Am. J. Med. **22**:784, 1957.
16. Cabrera, E. C., and Monroy, J. R.: Systolic and Diastolic Loading of the Heart; Electrocardiographic Data, Am. Heart J. **43**:669, 1952.

Ganglionic Blockade by Trimethidinium Methosulphate*

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Ganglionic blockade, or the use of drugs having equivalent effect, remains necessary for most severely hypertensive patients if a proper control is to be maintained over blood pressure levels. Now, there is a wide choice of agents falling into two main categories: quaternary ammonium compounds such as pentolinium (Ansolysen) and chlorisondamine (Ecolid), and secondary amines such as mecamylamine (Inversine, Mevasine) and pempidine (Perolysen).

Whereas individual patients may be distinctly more comfortable on some ganglion-blocking drugs which suit them individually than on others which do not, it cannot be stated yet that any single ganglion-blocking drug stands out as being consistently better than the others for a majority of patients. On the other hand, each of the well-known ganglion-blocking drugs is the drug of choice for at least a limited group of patients.

The purpose of this communication is to describe our experience over a period of 2 years and 3 months with a comparatively new ganglion-blocking drug, trimethidinium methosulphate (Fig. 1).

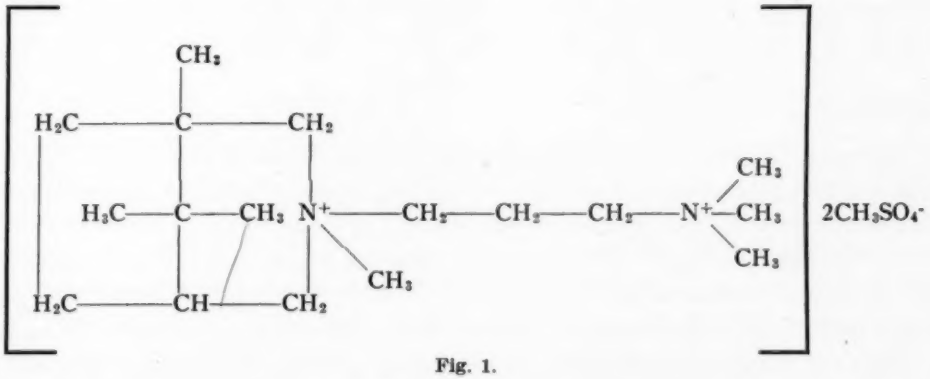

Fig. 1.

Klupp[1] described the typical ganglion-blocking properties of the drug in animals and mentioned the long duration, 6 to 12 hours, of its action. Clinical reports have been published by Kühns, Liebeskind and Müller,[2] Pillen,[3] Marx,[4]

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*Ostensin, WY 1395; Camphidonium, Ha 106.

Loos,[5,6] and Dunsmore, Dunsmore, Goldman, Elias and Warner.[7] The latter authors observed drug toleration which has not been noted in our clinic. Bär and Bachmann,[8] in a hemodynamic study, described the occurrence of a decrease in stroke and minute volumes.

Until trimethidinium methosulphate, an asymmetric bis-quaternary compound, became available, a consistent difference between quaternary ammonium compounds and hypotensive amines was that the former were incompletely, and the latter almost completely, absorbed from the alimentary tract; the former caused drug toleration, whereas the latter caused little or no drug toleration. Trimethidinium methosulphate resembles the quaternary ammonium compounds pharmacologically in that it is incompletely absorbed from the alimentary tract, but, as will be seen, it resembles the secondary amines in causing little or no drug toleration. Its practical value as a ganglion-blocking drug is discussed.

CLINICAL MATERIAL

Thirty-two patients have had clinical trials with trimethidinium methosulphate and periods of treatment up to 2 years and 3 months. Nine patients have been on continuous treatment for between 12 and 27 months.

TABLE I. RANGE OF EFFECTIVE DOSAGE (MG.) OF TRIMETHIDINIUM METHOSULPHATE

	APPROXIMATE TIME OF ADMINISTRATION		
	8 A.M.	2 P.M.	10 P.M.
Lowest effective dose	15	0	30
Mean effective dose	109	44	125
Highest effective dose	280	0	280
Highest dose only partly effective	270	140	270

RESULTS

Range of Effective Dosage of Trimethidinium Methosulphate.—In the 32 patients treated, attempts were made to bring the trough of the fall in blood pressure to normal or near normal levels, usually about 135/75 mm. Hg. Table I sets out the lowest, highest, and mean effective doses found necessary in order to accomplish this. The highest dose which was found to be only partly effective in reducing the blood pressure (trough blood pressure 172/98 mm. Hg) is also given.

Effect of Posture on the Hypotensive Action of Trimethidinium.—The effect of posture differs in no distinctive way from the action of other ganglion-blocking drugs. The extent of the postural fall relative to the nonpostural fall in blood pressure varies from one individual to another (Table II).

Effect of Fall in Blood Pressure on Pulse Rate.—The effects of trimethidinium on the pulse rate are variable but usually unimportant. Sometimes the rate decreases with the fall in blood pressure, and sometimes it increases. Changes seldom exceed 15 beats per minute and ordinarily are much less.

Effect of Chlorothiazide on the Fall in Blood Pressure Due to Trimethidinium.—Our present experience has been that the sensitivity to all of six ganglion-blocking drugs is increased by the addition of 0.5 Gm. of chlorothiazide twice daily to the regimen, together with 1 Gm. daily of potassium chloride. Enhancement of the action of ganglion-blocking drugs is present even when chlorothiazide alone has led to no significant reduction in the blood pressure. Trimethidinium is no exception, and the effect upon blood pressure levels of its combination with chlorothiazide is set out in Table III.

Absence of Significant Drug Toleration on Repeated Administration.—The occurrence of or failure to develop drug toleration was judged by the repetition of all-day tests under comparable conditions, the doses being administered orally and adjusted so as to induce similar falls in blood pressure with the patients in the standing posture. In 8 out of 16 patients the repeated administration of trimethidinium, usually over a period of a month and sometimes for several months, led to neither an upward nor a downward trend in the effective dose as judged by

TABLE II. EFFECT OF POSTURE ON THE HYPOTENSIVE ACTION OF TRIMETHIDINIUM METHOSULPHATE

PATIENT NUMBER	BLOOD PRESSURE (MM. Hg) BEFORE			BLOOD PRESSURE (MM. Hg) AFTER		
	LYING	SITTING	STANDING	LYING	SITTING	STANDING
H1051	208/124	196/130	200/132	150/98	132/86	130/90
H1220	232/140	212/120	202/112	168/104	152/92	140/84
H261	176/100	182/106	172/102	117/66	108/64	104/62
H1209	224/130	222/134	198/132	194/118	160/106	120/84
H1244	200/120	180/116	186/118	200/118	180/112	162/110
H1229	224/124	212/114	208/108	172/102	168/90	154/82
H1219	188/108	180/110	178/108	168/98	164/106	120/108
H313	238/112	220/110	190/94	160/64	148/62	122/54
H1208	194/118	182/110	186/112	156/100	140/94	132/94
H1135	246/118	224/110	216/106	194/96	160/86	138/68
H1077	192/80	192/74	186/76	150/60	146/66	134/58

TABLE III. EFFECT OF CHLOROTHIAZIDE ON THE REDUCTION OF BLOOD PRESSURE BY TRIMETHIDINIUM*

PATIENT NUMBER	BEFORE ADMINISTRATION OF CHLOROTHIAZIDE			DURING ADMINISTRATION OF CHLOROTHIAZIDE		
	DOSE OF TRIMETH-IDINIUM (MG.)	TROUGH BLOOD PRESSURE (STANDING)	AVERAGE DAY PRESSURE (STANDING)	DOSE OF TRIMETH-IDINIUM (MG.)	TROUGH BLOOD PRESSURE (STANDING)	AVERAGE DAY PRESSURE (STANDING)
H1264	120, 60, 120	134/80	150/86	100, 40, 100	116/67	145/83
H1209	140, 40, 140	152/106	191/128	140, 0, 160	106/74	117/78
H357	80, 10, 100	176/92	190/102	80, 0, 100	110/75	161/95
H1229	140, 40, 140	110/76	140/85	100, 0, 100	104/78	117/86

*The three doses of trimethidinium are usually administered at 8 A.M., 2 P.M., and 10 P.M.

all-day tests at our Hypertensive Clinic. In 5 patients the trend was for an increase and in 3 for a decrease in dosage level as compared with the first administration, which caused a fall in the blood pressure to a near normal level in the standing posture. In these patients, however, the effective dose was in no case doubled in those showing an increase, and in no case was it halved in those showing a decrease. It is quite clear that drug toleration if present at all is slight in degree and is of no practical concern in dosage regulation.

Side Effects of Trimethidinium Methosulphate.—As with all other ganglion-blocking drugs the administration of trimethidinium methosulphate in doses sufficient to cause distinct hypotension will lead also to parasympathetic side effects. If the parasympathetic side effects of different drugs are to be compared accurately, it is necessary to make the comparison in the same group of patients and at times when blood pressures have been reduced to a corresponding degree. Even so, because side effects often diminish in the course of several months, the comparison should be made at about the same time.

Some of the patients used in this initial study were chosen because we had failed previously to discover a comfortable regimen for them, or because, although comfortable in most ways, they desired relief from a particular side effect, such as blurred vision, and the drug was judged by its capacity to reduce blood pressure without causing the particular discomfort complained of.

Of the 32 patients, 5 are not considered from the standpoint of side effects because the available data were insufficient. Of the remaining 27 patients, 20 were well controlled as regards blood pressure levels without being much disturbed by side effects, and 7 were regarded as unsatisfactory from the standpoint of side effects in that when doses were large enough to reduce the blood pressure (standing posture) to near normal levels in the trough of the fall in blood pressure, the side effects were prominent or occasionally prohibitive.

Of the 7 patients with unsatisfactory responses, 2 had never been satisfactory on any regimen and one other had never tolerated an orally administered ganglion-blocking drug. Of the remaining 4 patients, 3, when on trimethidinium, complained of much visual blurring before the blood pressure was sufficiently reduced, and one of these 3 complained also of nausea. The remaining patient complained of diarrhea.

Of the 20 patients considered to respond satisfactorily, 12 did very well in that side effects, mainly blurring of vision and dry mouth, were slight and for the most part had not been complained of spontaneously. The patients felt well. Of these 12 patients, 4 had no additional drug, 5 had also a rauwolfia alkaloid, 2 had rauwolfia alkaloid and chlorothiazide, and 1 had chlorothiazide but no rauwolfia alkaloid. Eight additional patients were satisfactory in that side effects, although not negligible, were easily tolerated. Only 4 out of the 8 patients had any adjuvant therapy, and what slight difference appeared to distinguish the 8 satisfactory from the 12 very satisfactory might have depended to some extent on the use of adjuvant therapy.

Five patients expressed a preference for some other drug. Visual blurring was more prominent at the same or at a higher blood pressure level on trimethidinium

than on pentolinium in 3 patients, than on mecamylamine in 1, than on pempidine also in 1 patient.

Four patients expressed a preference for trimethidinium over one or several other ganglion-blocking drugs. One patient who had previously been comfortable only on injected pentolinium was easily controlled by oral trimethidinium. One patient had less dry mouth on trimethidinium than on pentolinium. The 2 patients whose case histories are set out below found that trimethidinium solved a major problem in management and, for them, was clearly superior to any other ganglion-blocking drug tried.

Patient H261.—This 65-year-old woman, retinal Grade 2, who did not complain of diarrhea before she took ganglion-blocking drugs, used to have 5 to 8 bowel movements daily when the blood pressure level was controlled by hexamethonium, pentolinium, and other ganglion-blocking drugs on clinical trial only. This was presumably due to a predominant effect upon the sympathetic innervation of the bowel, because diarrhea was prompt and there was no antecedent constipation. On trimethidinium she promptly became entirely free from the complaint and has remained so since.

Patient H357.—This 58-year-old woman, originally retinal Grade 4, maintained only a moderately satisfactory control over the blood pressure level by a complicated regimen which included pentolinium, rescinnamine, and Hydralazine. The regimen was greatly simplified and improved by the use of trimethidinium in combination with rescinnamine, and further improvement with loss of side effects was obtained by the addition of chlorothiazide (0.5 Gm. b.d.).

No unexpected side effects were encountered in any of our patients and no long-term toxicity was observed.

SUMMARY

Trimethidinium methosulphate is in most respects a typical quaternary ganglion-blocking drug of the better sort. However, its advantage over most other quaternary drugs is that its continued administration does not lead to significant drug toleration. In general, side effects are mild or moderate but some visual blurring is common.

For generous supplies of trimethidinium the author is indebted to Wyeth International Limited (for Ostensin) and to C. H. Boehringer Sohn (for camphidonium). The expenses of this work have been defrayed by the Medical Research Council of New Zealand.

REFERENCES

1. Klupp, H.: Pharmakologische Untersuchung eines neuen Ganglienblockers mit langer Wirkungsdauer, N-(-Trimethylammoniumpropyl-N-methyl-camphidinium-dimethylsulfat (HA-106), Aerztliche Forschung (Drug Res.) **7**:123, 1957.
2. Kühns, K., Liebeskind, H., and Müller, W.: Zur Behandlung der Hochdruckkrankheit mit Ganglienblockern; klinische Prüfung einer neuen bisquaternären Verbindung (Ha 106), Aerztliche Wochenschrift **11**:1053, 1956.
3. Pillen, D.: Zur Kombinationsbehandlung des Hochdrucks, Aerztliche Forschung **11**:607, 1957.
4. Marx, H.: Ganglienblocker bei akuter Herzinsuffizienz, Die Medizinische **11**:444, 1958.
5. Loos, H.: Zur Behandlung der chronischfixierten Hypertonie mit einem neuen langwirkended Ganglienblocker, Die Medizinische **23**:868, 1957.
6. Loos, H.: Zur hausärztlichen Behandlung der chronische fixterten Hypertonie, Therapie der Gegenwart **96**:451, 1957.
7. Dunsmore, R. A., Dunsmore, L. D., Goldman, A., Elias, M., and Warner, R. S.: Treatment of Ambulatory Hypertensive Patients with Trimethidinium Methosulfate, Am. J. M. Sc. **236**:483, 1958.
8. Bär, C. G., and Bachmann, K.: Hämodynamische Untersuchungen mit einem neuen Ganglienblocker (Camphidonium), Ztschr. Kreislaufforsch. **46**:670, 1957.

Experimental and Laboratory Reports

Role of Acute Myocardial Hypoxia and Ischemic-Nonischemic Boundaries in Ventricular Fibrillation

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The frequent occurrence of ventricular fibrillation (VF) subsequent to the occlusion of a major coronary artery has been attributed to the discharge of impulses from the border zone between the ischemic and the well-perfused areas of the ventricular myocardium.[1] According to Brofman, Leighninger and Beck,[2] myocardial ischemia produced changes in the electrical state of the muscle, thus setting up currents between the ischemic and the nonischemic regions. When these currents were of sufficient magnitude, ectopic discharges from the border zones occurred. Such impulses, particularly when accelerating, may lead to fibrillation. The above-mentioned authors postulated that the potentials were related to an inequality in the degree of oxygenation of the myocardium. Hence, the term "current of oxygen differential" has been proposed.

Fatal hypoxic hypoxia and asphyxia practically never induced fibrillation of the ventricles, thereby supporting the concept of boundaries.[3,2] Under these circumstances the terminal event in the ventricles was progressive dilatation and weakening of contractions, leading to mechanical asystole and, finally, cessation of electrical activity. The explanation given was that such hypoxia, being diffuse throughout the myocardium, presented no boundaries[3] or "trigger zones"[2] to fire ectopic impulses. The heart was said to be electrically stable. In such a cyanotic beating heart, perfusion of a coronary artery with oxygenated blood may lead to VF ("reverse trigger").[2]

One would anticipate that interruption of the entire coronary arterial supply to the myocardium should not induce VF. It is the purpose of the present study to report the manner in which cardiac function fails when the right (including the accessory) and the left coronary arteries are simultaneously ligated

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close to their origin. As a control, a second series of experiments was conducted in which the two coronary arteries were dissected and generalized hypoxia was produced by the administration of 100 per cent nitrogen in the inspired air.

METHODS

Mongrel dogs weighing 7 to 15 kilograms were anesthetized with intravenous sodium pentobarbital. The ECG (Lead II) and femoral arterial pressure, using a Statham transducer, were registered on a Sanborn two-channel, direct-writing recorder. Control readings were taken with the animal in the supine position. Then under artificial respiration with an Emerson resuscitator connected to the compressed air line, the chest was opened by a longitudinal incision of the sternum. The thoracic portion of the phrenic nerves was removed and the pericardium incised. The lungs and heart were covered with gauze moistened with saline, and the edges of the pericardium were sutured to the chest wall, making a cradle for the heart. A second ECG and pressure recording were made.

The right coronary artery was then dissected as close to its origin as possible and a loose nylon ligature (20-pound test casting line) passed around it. Subsequently, the accessory right coronary artery, which arises either independently from the aorta or as the first branch of the right,[4,5] was dissected and included in the same ligature. Another ECG and arterial pressure record were taken.

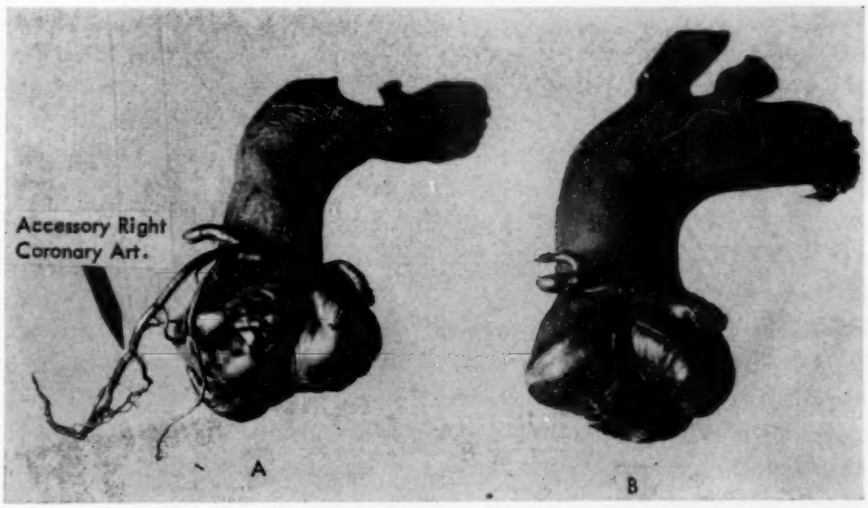

Fig. 1.—*A*, Cast of aorta showing unoccluded accessory right coronary artery. *B*, Similar cast showing satisfactory occlusion of all coronary arteries.

After turning the animal to its right and cutting between the appropriate ribs, the left coronary artery was dissected and a nylon ligature passed under it. The heart was uncovered and the ECG and arterial pressure were recorded. Then the two ligatures were tied simultaneously to stop all arterial inflow to the myocardium.* Records were taken continuously until VF or ventricular asystole supervened. Artificial respiration was continued until the heart failed to pump blood.

The adequacy of occlusion was determined by removing the heart, washing it in tap water, and injecting the aorta with latex. Four hours later the heart was placed in concentrated hydro-

*In one experiment the vagi were cut in the neck and the upper five thoracic ganglia removed bilaterally prior to the occlusion of the coronaries.

chloric acid to digest the soft tissues (Fig. 1). Tiny vessels supplying the aortic wall or adipose tissue around the right coronary artery were detected in some of these casts. Because these vessels were proximal to the occlusion and did not supply the ventricular myocardium, such experiments were considered technically satisfactory.

Since factors such as cardiac exposure, artificial respiration, manipulation of the heart, etc., might favor VF, a second series of experiments was performed. The two major arteries were dissected as before, but instead of ligating them, acute generalized hypoxia was produced by the inhalation of 100 per cent nitrogen. In these experiments a Starling pump was used to inflate the lungs and 100 per cent N_2 was administered with the use of a demand valve. (The design of the Emerson resuscitator previously employed did not permit pure nitrogen to reach the lungs.)

Finally, in some intact dogs, acute hypoxia was induced by the inhalation of 100 per cent N_2 (3 experiments), or 100 per cent carbon monoxide (1 experiment), or 50 per cent carbon monoxide in oxygen (1 experiment). The carbon monoxide was administered from a Benedict-Roth metabolimeter.

RESULTS

Occlusion Experiments.—From a total of 30 attempts, only 10 were satisfactory occlusions. In many of the unsuccessful experiments the right accessory coronary was unoccluded (Fig. 1,*A*) or the vessels ruptured during the dissection.

Table I presents the data of the 10 satisfactory occlusions. Opening the chest resulted in a marked fall in arterial pressure, presumably due to the hyperventilation that was unavoidable with the use of the Emerson resuscitator. The ECG (Lead II) did not show striking changes. In most experiments the T wave was inverted initially and underwent minor or no changes on opening of the chest. No significant changes in arterial pressure occurred following the dissection of the coronary arteries. The ECG exhibited no change or minor alterations in the T wave or S-T segment. In one experiment, pulsus alternans was observed.

Soon after the complete arrest of the arterial flow to the entire myocardium, ventricular contractions became weaker, dilatation of the heart occurred, and arterial pressure declined rapidly to very low levels. Arrhythmia in the form of ventricular premature beats then ensued and heralded the onset of fibrillation. In 9 experiments, VF supervened after an average of 3.76 minutes. In one experiment the ventricles gradually failed to contract, and, finally, ventricular electrical activity ceased entirely (asystole).

The ECG changes after occlusion consisted, in general, of alterations in the T wave and S-T segment and then widening of the QRS complex. Fig. 2 shows the usual pattern observed before the onset of ventricular premature beats.

Hypoxia Experiments.—

After dissection of the right and left coronary arteries: The results of these experiments were so uniform that only a few were carried out (Table II). Ventricular fibrillation never occurred. The ventricles became markedly cyanotic and dilated. There was an initial rise in arterial pressure, which then declined gradually as the myocardial contractions became weaker, attaining very low levels when ventricular ejection ceased altogether. Invariably, the ventricles

stopped in asystole. The ECG showed marked alterations, with very large T waves and various degrees of atrioventricular block. Changes in heart rate were, first, sinus bradycardia followed by tachycardia and, finally, marked slowing with the onset of block. In one experiment, prior to hypoxia there was pulsus alternans which disappeared during hypoxia. The arterial pressure pulse ceased after 7 minutes of hypoxia, whereas electrical activity continued for about 28 minutes. The muscle overlying the ventricular septum was most persistent in showing very weak, hardly perceptible contractions which continued until the onset of electrical "asystole."

Closed chest: The experiments in which 100 per cent nitrogen or carbon monoxide was inhaled gave results essentially similar to the open-chest series. Ventricular fibrillation never occurred. Mechanical asystole supervened in about 8 minutes, whereas electrical activity, rhythmic in character, persisted for about 29 minutes from the beginning of hypoxia.

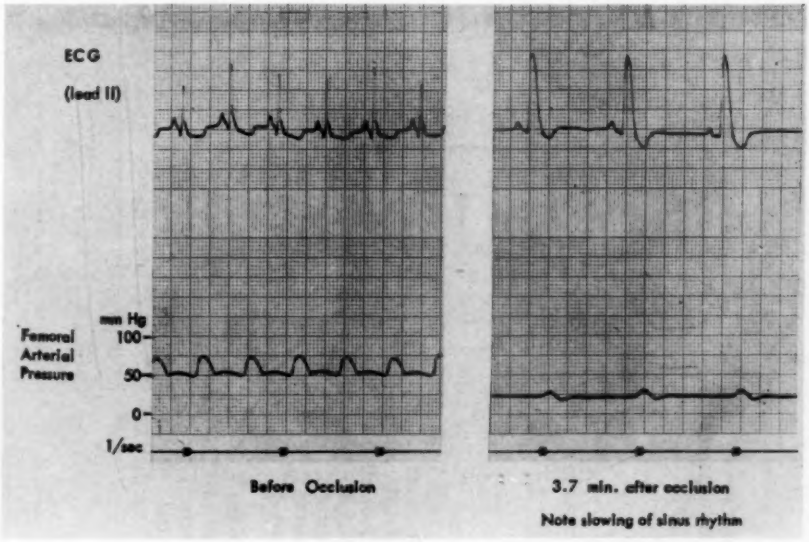

Fig. 2.—Effect on ECG and arterial pressure of sudden interruption of the entire coronary arterial flow. This pattern occurred before the onset of ventricular ectopic beats and fibrillation.

DISCUSSION

The concept that VF subsequent to the occlusion of a major coronary artery is related to the "boundary" between the ischemic and perfused areas of the ventricular myocardium cannot be substantiated by the results obtained in this study. Apparently, such border zones are not essential for ectopic discharges. In coronary occlusion the factor(s) responsible for such discharges remains (remain) quite obscure. The fundamental mechanism underlying ectopic rhythms is still very poorly understood and remains as a major stumbling block in gaining insight into many problems of disturbed cardiac function.

TABLE I. INTERRUPTION OF ENTIRE CORONARY ARTERIAL FLOW

EXPERIMENT NUMBER	NATURAL BREATHING WITH CLOSED CHEST		CHEST AND PERICARDIUM OPEN (EMERSON RESUSCITATOR)		AFTER DISSECTION OF RIGHT CORONARY		AFTER DISSECTION OF BOTH CORONARIES		TOTAL CORONARY OCCLUSION		
	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	TERMINAL VENTRICULAR EVENT	ONSET OF TERMINAL EVENT (MIN.)	FEMORAL PRESSURE PRIOR TO TERMINAL EVENT (MM. Hg)
10.		Normal		Normal		Inverted T		Inverted T	Asystole	30+	
21.	140	Inverted T	55	Sloping R-T segment	60	Sloping R-T segment	55	Depressed R-T segment	Fibrillation	6.9	10
22.	150	Normal	60	Wide QRS Inverted T	60	Wide QRS Inverted T	65	Wide QRS Inverted T	Fibrillation	4.0	15
26.	125	Inverted T	60	Inverted T	67	Inverted T	100	Inverted T	Fibrillation	2.6	20
27.	135	Inverted T	105	Inverted T	95	Inverted T	100	Inverted T	Fibrillation	6.0	8
29.	155	Normal	95	Inverted T	90	Inverted T	80*	Inverted T	Fibrillation	3.3	8
30.	165	Inverted T Elevated S-T	65	Inverted T	65	Inverted T	60	Inverted T	Fibrillation	3.15	12
32.	100	Inverted T	80	Inverted T Elevated S-T	60	Inverted T Elevated S-T	75 (alternans)	Small inverted T	Fibrillation	2.54	10
34.	160	Inverted T	70	Inverted T	80	Inverted T	65	Inverted T	Fibrillation	2.66	10
35.	130	Normal	110	Normal	85	Depressed S-T segment	60	Depressed S-T segment	Fibrillation	2.75	10
Mean	140		78		74		73			3.76 (excluding No. 10)	11

*Denervation of heart before dissection of left coronary artery.

TABLE II. ACUTE HYPOXIA AFTER DISSECTION OF THE RIGHT AND LEFT CORONARY ARTERIES

EXPERIMENT NUMBER	NATURAL BREATHING WITH CLOSED CHEST		CHEST AND PERICARDIUM OPEN (STARLING PUMP)		AFTER DISSECTION OF RIGHT CORONARY		AFTER DISSECTION OF BOTH CORONARIES		INHALATION OF 100 PER CENT N_2			
	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	MEAN FEMORAL PRESSURE (MM. Hg)	ECG (LEAD II)	TERMINAL VENTRICULAR EVENT	MECHANICAL ASYSTOLE		ONSET OF ELECTRICAL "ASYSTOLE" (MIN.)
										ONSET (MIN.)	FEMORAL PRESSURE (MM. Hg)	
36.	112	Inverted T	110	Inverted T	115	Inverted T	95	Inverted T	Asystole	9.3	5	46.0
37.	160	Normal	135 (alternans)	Inverted T	145 (alternans)	Upright T	105 (alternans)	Inverted T	Asystole	7.5	7	19.2
38.	125	Inverted T	115	Inverted T	125	Upright T	75	Upright T Depressed S-T	Asystole	4.7	5	19.1
Mean	132		120		128		92			7.2	6	28.1

Beck and associates[2] have propounded the concept of "current oxygen differential," which seems inadequate to explain why ischemia of the entire myocardium should result in fibrillation. One may postulate that different myocardial fibers may have different requirements for oxygen, and that after arrest of the entire coronary flow, oxygen differentials may arise which may ultimately lead to fibrillation. Such an explanation would have difficulty in accounting for the absence of differentials in hypoxic hypoxia, unless one assumes that the coronary vascular bed in various areas of the myocardium responds differently to hypoxemia. The role of Thebesian channels in perfusing the myocardium when pressure in the coronary arterial system is reduced to about zero was studied in the heart-lung preparation by Stella.[6] He found no flow in the coronary arteries or coronary sinus when the heart was performing different types and degrees of work. However, this finding does not rule out the possible diffusion of oxygen from the ventricular blood (especially from the left) into the subendocardial layers of the myocardium. Wiggers[7] and Stella[6] have presented evidence that various compounds can gain access to the myocardium by such a process. A suggestive approach to the evaluation of the interesting hypothesis of Beck and associates would be to record the oxygen tension in different parts of the ventricular myocardium under conditions such as hypoxic hypoxia, asphyxia, interruption of the entire coronary flow, etc. Technical difficulties prevented us from conducting such studies.

Harris and co-workers[8] suggested that ectopic foci arise at the boundary of ischemic myocardium as a result of the excitatory action of potassium released from the ischemic muscle. This explanation cannot be entirely true, at least as far as the site of action of the released potassium is concerned. However, the release of potassium from ischemic heart muscle may be involved in the setting up of ectopic impulses. The studies of Cherbakoff, Toyama and Hamilton[9] seem to support such a role. Siebens and associates[10] have shown that elevation of serum potassium concentration lowers the ventricular diastolic threshold.

The observation that acute fatal hypoxic hypoxia, anemic hypoxia, and asphyxia did not induce VF suggested that the VF of generalized myocardial ischemia was not related to the disturbed gaseous homokinesis of the myocardium. It is conceivable that the factor(s) favoring VF was (were) a disturbance in the nongaseous exchanges across myocardial capillaries and muscle cells. This can be either (1) a deprivation of a substance or substances in the arterial blood, and/or (2) a lack of removal of some nongaseous product or products from the ischemic tissue. Some evidence against this possibility may be derived from the recent studies of Burns and his co-workers,[11] who perfused the coronaries with a humidified gas mixture consisting of 5 per cent CO_2 in 95 per cent O_2. Isolated rabbit hearts perfused in this way kept beating for several hours without fibrillating. However, these investigators' experimental conditions were not similar to ours in that the change from coronary blood flow to coronary gas flow was neither sudden nor accomplished while the heart was performing external work. It would be of interest to determine the effect of suddenly perfusing the coronaries with oxygen-free plasma instead of oxygenated blood.

Cardiac surgeons, operating under hypothermia, believe that the diminished coronary flow subsequent to venous inflow occlusion played a role in precipitating VF. In support of this was the fact that in hypothermia with venous occlusion, perfusion of the coronaries with oxygenated blood markedly reduced the incidence of VF.[12-14] It was difficult to reconcile this observation with the reports that hemorrhagic hypotension[3] and acute fatal hemorrhage[15] did not lead to VF. On the other hand, results under normothermic conditions should not be applied to the hypothermic state without reservation. To our knowledge, no data are available to show the mode of arrest of the hypothermic dog heart subjected to fatal asphyxia or hypoxia.

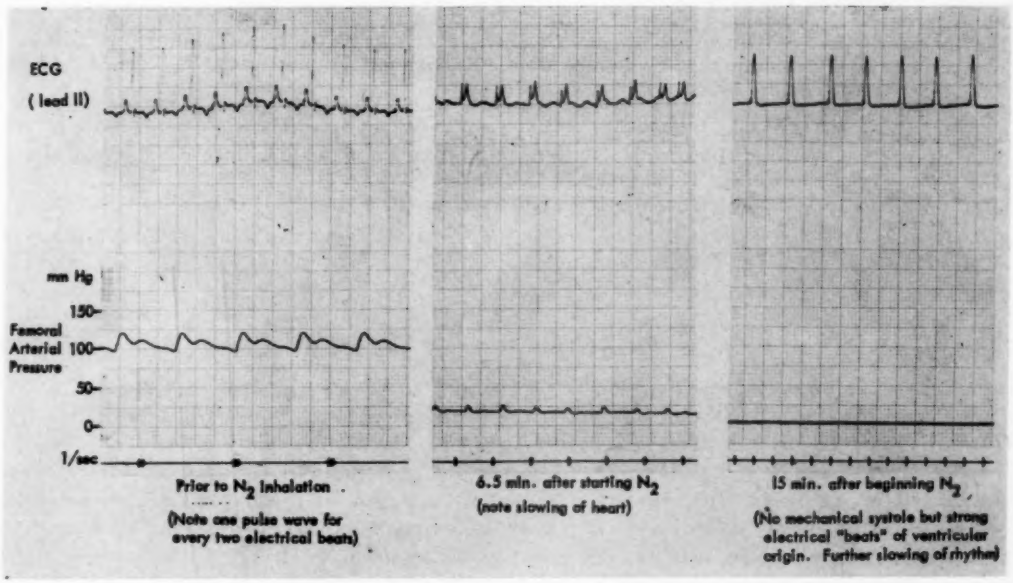

Fig. 3.—Changes in ECG and arterial pressure subsequent to the inhalation of 100 per cent N_2 after dissection of the two coronary arteries. Note the rhythmic ventricular deflections in the absence of mechanical systole on the pressure tracing.

In the hypoxia experiments the authors were impressed by the discrepancy between the amplitude of the electrical deflections and the mechanical contractions of the ventricles. Although the widening of the QRS complex is indicative of the poor state of the myocardium, such signs of impairment of function may not be immediately apparent. The cessation of electrical activity occurred long after the complete failure of ventricular ejection and the fall of arterial pressure (Fig. 3). Apparently, the aerobic energy required for the processes of repolarization and depolarization was much less than that for the lengthening and shortening of the molecules of actomyosin and meromyosins. These observations emphasize that the ECG cannot be relied upon in the clinical diagnosis of cardiac "arrest" when this is due to asystole. The fact that other methods are being sought for the immediate diagnosis of cardiac "arrest" indicates that clinicians realize the shortcomings of the ECG.[16]

We wish to thank Mrs. Elsie Nibbelink and Mr. Paul Willard for their technical assistance.

REFERENCES

1. Harris, A. S., and Guevara Rojas, A.: Exper. Med. & Surg. **1**:105, 1943.
2. Brofman, B. L., Leighninger, D. S., and Beck, C. S.: Circulation **13**:161, 1956.
3. Harris, A. S.: Am. Heart J. **35**:895, 1948.
4. Moore, R. A.: Am. Heart J. **5**:743, 1930.
5. Pianetto, M. B.: Am. Heart J. **18**:403, 1939.
6. Stella, G.: J. Physiol. **73**:36, 1931.
7. Wiggers, C. J.: Am. J. Physiol. **90**:558, 1929.
8. Harris, A. S., Bisteni, A., Russell, R. A., Brigham, J. C., and Firestone, J. E.: Science **119**:200, 1954.
9. Cherbakoff, A., Toyama, S., and Hamilton, W. F.: Circulation Res. **5**:517, 1957.
10. Siebens, A. A., Hoffman, B. F., Ensen, Y., Farrell, J. E., and Brooks, C. McC.: Am. J. Physiol. **175**:1, 1953.
11. Burns, B. D., Robson, J. G., and Smith, G. K.: Canad. J. Biochem. & Physiol. **36**:499, 1958.
12. Shumway, N. E., Gliedman, M. L., and Lewis, F. J.: J. Thoracic Surg. **30**:598, 1955.
13. Edwards, W. S., Simmons, E., Lombardo, C. R., Bennett, A., and Bing, R. J.: A.M.A. Arch. Surg. **71**:853, 1955.
14. Lombardo, T. A., Radigan, L. R., and Morrow, A. G.: Circulation Res. **5**:22, 1957.
15. Negovski, V. A.: Am. Rev. Soviet Med. **2**:491, 1944-45.
16. Edmark, K. W., and Harkins, H. N.: Surgical Forum, Vol. 7, 42nd Clinical Congress, Chicago, American College of Surgeons, 1957, p. 290.

Pulmonary Arterial and Reticuloendothelial Modifications Induced by Serotonin in the Rabbit and in the Rat

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In rabbits, pulmonary[1] and coronary[2] arteriosclerosis due to serotonin is interesting since the changes in the arteries were produced by an endogenous substance and the actual mechanism of the lesions may have been of humoral type. We report here the species-difference of arteriosclerosis due to serotonin in the rabbit and the rat.

METHOD

A group of rats, weighing 180 to 200 grams, were treated with serotonin for 35 days in doses of 1 mg. every 12 hours. Three groups of rabbits, weighing 1,600 kilograms, were treated with serotonin in doses of 5 mg. every 12 hours—the first group for 3 days, the second group for 35 days, and the third group for 90 days. All of the animals were males; they were kept on a standard diet, received the drug subcutaneously, and were killed at the end of the treatment. The thoracic contents were removed and the lungs were distended via trachea to their normal size with formol-saline, and the whole was placed in formol-saline to fix. Blocks were taken from various parts of all lobes and paraffin sections were stained with hematoxylin and eosin, with Weigert's elastic tissue stain, and with Hopa's connective tissue stain; as needed, lung sections were also stained with the periodic acid-Schiff reagent. At least one block from each animal was cut frozen and stained with Baker's phospholipid method and Sudan III.

RESULT

In the rabbits treated with serotonin for 3 and 35 days the elastic arteries of the lungs were not involved. Intimal lesions were observed occasionally in a few muscular arteries and arterioles; the intimal coat showed a mild fibroblastic proliferation which developed small cushions in the lumen. The endothelial cells appeared radially to the lumen and showed elongated nuclei. In the third group of rabbits the intimal changes were more diffuse and severe. The fibro-elastic proliferation produced a remarkable thickening of the intimal coat, with cushions in the lumen of large pulmonary arteries (Fig. 1), and reduced the lumen of medium-sized and small arteries in varying degrees (Figs. 2-4). The

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walls of muscular arteries were thickened because of mild hypertrophy. In the arteries with intimal lesions the deposits of mucopolysaccharides in the subendothelial layers were revealed by the periodic acid-Schiff reaction. No "fibrinoid necrosis" was noted. No stainable fat was seen in any of the pulmonary vessels.

In the rats treated with serotonin the lesions were very scarce and much less severe. Only some muscular arteries showed a mild fibroelastic hyperplasia which developed small cushions in the lumen.

In the rabbits and in the rats some sections of the lungs revealed reticuloendothelial proliferations in the alveoli and septa; the cells showed large reticular cytoplasm and mytosis (Fig. 5). In this infiltration numerous foam cells revealed cytoplasm stuffed with the Sudan-stainable fats and the phospholipids.

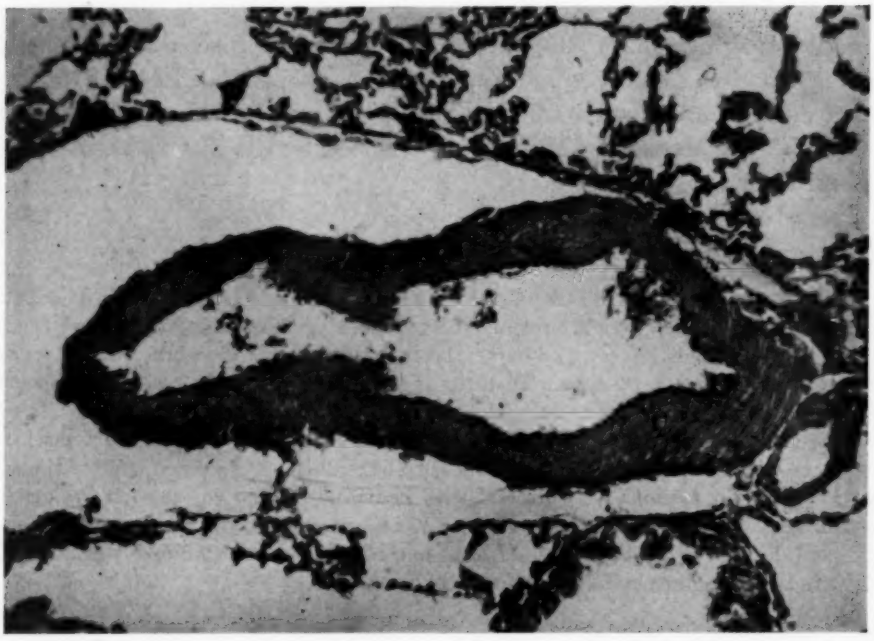
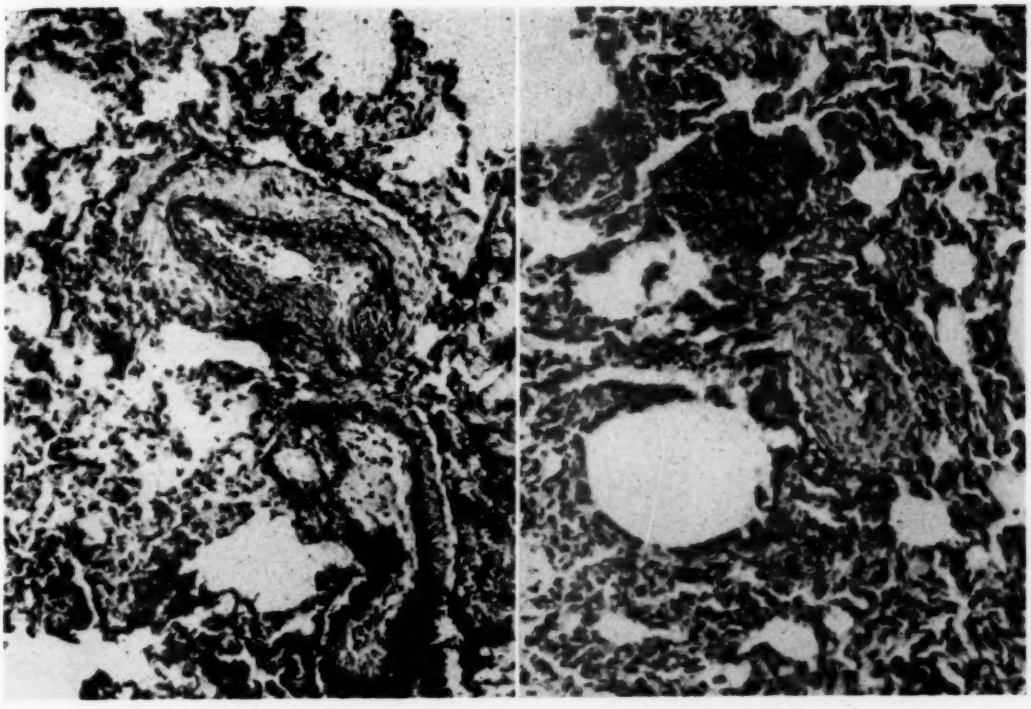


Fig. 1.—A large pulmonary artery of a rabbit with fibroelastic hyperplasia of the intima which developed cushions in the lumen.

COMMENT

The morphologic changes due to serotonin were observed chiefly in the intima of the rabbit's pulmonary arteries. These changes were already apparent after 35 days of treatment. In experimental and clinical observations the fibrous intimal changes of arteries have until now been attributed either to effects of the blood pressure or to organization of blood clots in the intimal coat. Serotonin causes an increase in the pulmonary pressure, but it seems quite unlikely that variable hemodynamic changes are able to produce intimal thickening after 3 or 35 days. Our findings cannot be explained by a mechanical factor, and the actual mechanism of structural changes observed in the pulmonary arteries is



Figs. 2, 3, and 4.—Small pulmonary arteries of a rabbit with fibroelastic hyperplasia of intima and asymmetrical reduction of lumen.

unknown. Histamine is not able to induce intimal changes such as serotonin does.[3] Therefore, the two amines show different effects; the suggestion of serotonin acting as a histamine-liberator is no longer tenable.

It is well to emphasize that the lesions are caused by an endogenous substance and are characterized by the fibrous hyperplasia of intima and the deposits of mucopolysaccharides in the subendothelial layers. The subendothelial deposits of mucopolysaccharides might be the beginning of lesions, but the fibroblastic proliferation of intimal tissue and reticuloendothelial infiltrations of the septa and alveoli might represent the effect of a direct action of serotonin on connective tissue. The arterial lesions of the rats treated with serotonin were not significant, and this is in agreement with Mallory's finding.[4] This difference may be an important aspect of the differing action of serotonin in different species.

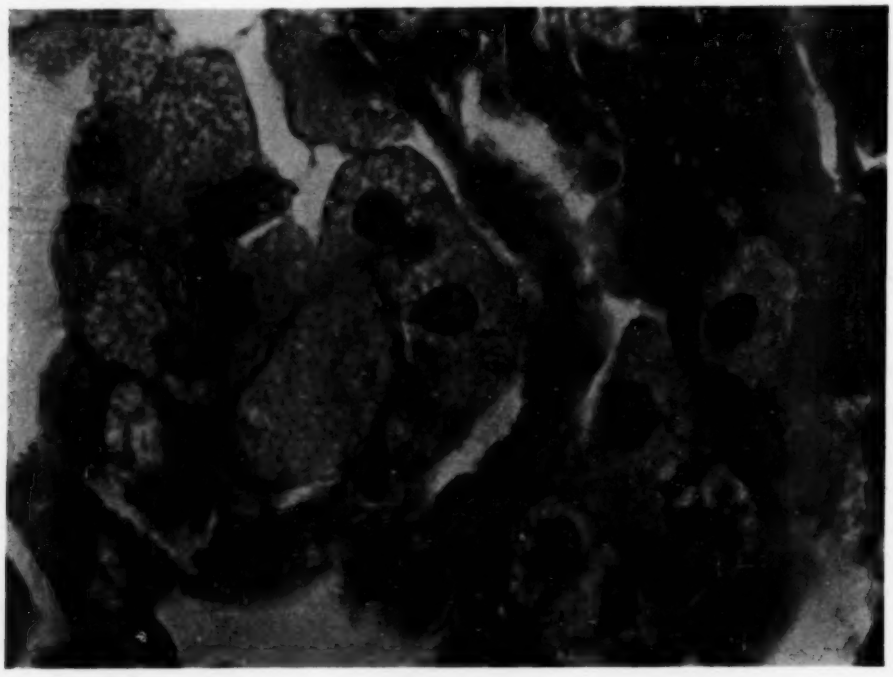


Fig. 5.—Reticuloendothelial proliferation in lung of rabbit.

SUMMARY

Prolonged treatment with serotonin produced pulmonary arteriosclerosis in the rabbit, very few modifications of the pulmonary arteries in the rat, and reticuloendothelial proliferations with foam cells, which revealed cytoplasm stuffed with the Sudan-stainable fats and the phospholipids.

REFERENCES

1. Rossi, P., and Zamboni, L.: Nature **181**:1216, 1958.
2. Rossi, P., Mascagni, M. T., and Spanò, G.: Boll. Soc. Ital. Cardiologia 249, 1957.
3. Rossi, P., Motolese, M., and Zamboni, L.: Arch. Ital. An. Istologia Patologica (In press.)
4. Mallory, G. K., MacDonald, R. A., and Roblins, S. L.: A.M.A. Arch. Path. **65**:369, 1958.

Experimental Evaluation of Systemic and Coronary Arterial Pressure Response Associated With Ligation of the Internal Mammary and Subclavian Arteries

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Distinct anatomic pericardiophrenic-coronary artery intercommunications have long been known to exist. It is only with the advent of bilateral internal mammary artery ligation, however, that these anastomoses have achieved theoretical functional significance. The favorable clinical results following bilateral internal mammary artery ligation recently reported by Battezzati[1] and Glover[2-5] have established a definite need for evaluation of the physiologic response to ligation of the internal mammary arteries.

Taber and Marchiaro[8] have reported consistent elevations of pressure in the subclavian arteries of dogs following bilateral internal mammary artery ligations. Sabiston and Blalock[7] reported increases in flow, backpressure, and backflow of varying magnitudes following ligation of the subclavian and/or internal mammary arteries in canine subjects. The latter authors, however, were unable to note any protection afforded to the heart following bilateral internal mammary artery ligation when challenged by ligation of the anterior descending coronary artery.

In attempting to develop a logical physiologic rationale for the procedure, one must accept the recognized fact that an increase in pressure gradients in a segment of the vascular system will be accompanied by an associated increase in volume flow per unit time in the same localized system, providing resistance to flow does not change. The physiologic explanation of the efficacy of bilateral internal mammary artery ligation proposed in support of the clinical application of this procedure to the management of occlusive coronary arterial disease is based on a postulated favorable alteration of arterial pressure gradients in the internal mammary-pericardiophrenic arterial system following internal mammary artery ligation.

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The proposed hypothesis offered is a logical one only if, following internal mammary artery ligation, it can be established that: (1) there is a definite rise in pressure in the proximal segment of the ligated internal mammary artery, (2) the high "end pressure" in the proximal segment of the ligated parent artery is transformed into "lateral pressure" which is directed into its branches (pericardiophrenic) resulting in an increased volume flow through them, and (3) the suggested rise in pressure is localized to the internal mammary-pericardiophrenic system, without an associated simultaneous rise of a similar magnitude in the systemic and coronary arterial pressure. In addition to the above three factors a fourth factor of significance is that the pericardiophrenic-superior phrenic circuit must be proved to be shared by the myocardium through its extracardiac communications with the pericardiophrenic arterial system.

The purpose of this communication is to present and discuss data acquired in an experimental evaluation of the systemic and coronary arterial pressure response associated with ligation of the internal mammary arteries in canine subjects. These studies were undertaken in an attempt to establish whether internal mammary artery ligation is followed by a demonstrable rise in pressure in the proximal segment of the internal mammary artery, whether the associated rise in pressure, if it occurs, is transmitted into branch arteries, and lastly, whether the rise in pressure, if it occurs, is localized to the internal mammary-pericardiophrenic system. A consideration of the presence of coronary communications with the pericardiophrenic-superior phrenic arterial system assumes little or no significance unless the former three factors can be shown to respond in a manner which would favor an increased flow in the internal mammary-pericardiophrenic arterial system, following internal mammary artery ligation.

PROCEDURE

Healthy mongrel dogs weighing 18 to 28 kilograms were used in this study. Anesthesia was induced with intravenous Nembutal in a dosage of 30 mg. per kilogram of body weight. Respiration was maintained with the aid of a cuffed endotracheal tube and a mechanical respirator, utilizing intermittent positive pressure. A left thoracotomy was performed in the first two groups of animals. Direct systemic intra-arterial pressures were measured using short polyethylene catheters introduced directly into the arteries. The catheters were connected to P23D Statham strain gauges which, in turn, were connected to a Gilson polygraph recording apparatus. Intracoronary arterial pressures were determined by introducing into the left anterior descending coronary artery a short beveled No. 20 needle connected to the above-described measuring and recording apparatus. Catheters and needles were introduced into the arterial systems with their open ends directed against the streamline of blood flow, in order to eliminate the variability occasioned by random positioning as well as the Bernoulli flow effects past a pressure measuring catheter whose orifice is directed along, rather than against, a streamline of flow.

Group I consisted of 10 dogs in which simultaneous pressure determinations were recorded from the internal mammary, subclavian, and femoral arteries. Pressures were first measured and recorded prior to, during, and subsequent to ligation of the left internal mammary artery. Pressures were then measured and recorded prior to, during, and subsequent to ligation of the left subclavian artery. Ligation of the internal mammary artery was performed in the second left intercostal space. Ligation of the subclavian artery was performed just distal to the origin of the internal mammary artery.

Group II consisted of 5 dogs in which simultaneous pressures were recorded in the subclavian and left anterior descending coronary arteries prior to, during, and subsequent to ligation of the left internal mammary and subclavian arteries.

Group III consisted of 5 dogs in which extrapleural bilateral internal mammary artery ligations were performed. Direct arterial punctures with No. 20 needles allowed simultaneous intra-arterial pressure determinations from the proximal and distal segments of the ligated arteries at periods of 2, 4, and 5 weeks following ligation of the arteries.

RESULTS

The findings in the animals of Group I revealed that there was a definite rise in the pressure in the proximal segment of the ligated internal mammary artery (Table I). The recorded rise in pressure was an average mean of 11.0 mm. Hg in the 10 animals. The maximum rise in mean pressure recorded was 14 mm. Hg,

TABLE I. MEAN INTRA-ARTERIAL PRESSURE RISE MEASURED SIMULTANEOUSLY FROM THE INTERNAL MAMMARY, SUBCLAVIAN, AND FEMORAL ARTERIES FOLLOWING LIGATION OF THE INTERNAL MAMMARY ARTERY

ANIMAL NUMBER	LIGATION OF INTERNAL MAMMARY ARTERY RISE IN MEAN PRESSURE (MM. Hg)		
	INTERNAL MAMMARY	SUBCLAVIAN	FEMORAL
1.	10	10	10
2.	7	6	6
3.	14	12	12
4.	12	12	14
5.	10	12	10
6.	9	9	8
7.	14	14	15
8.	12	12	13
9.	8	7	8
10.	14	16	16
Average	11.0	11.0	11.2

TABLE II. MEAN INTRA-ARTERIAL PRESSURE RISE MEASURED SIMULTANEOUSLY FROM THE INTERNAL MAMMARY, SUBCLAVIAN, AND FEMORAL ARTERIES FOLLOWING LIGATION OF THE SUBCLAVIAN ARTERY

ANIMAL NUMBER	LIGATION OF SUBCLAVIAN ARTERY RISE IN MEAN PRESSURE (MM. Hg)		
	INTERNAL MAMMARY	SUBCLAVIAN	FEMORAL
1.	12	13	12
2.	10	10	10
3.	14	14	15
4.	14	14	15
5.	12	12	11
6.	10	11	11
7.	15	15	16
8.	12	12	12
9.	7	6	7
10.	16	15	15
Average	12.2	12.2	12.4

whereas the minimum rise in mean pressure was only 7 mm. Hg, revealing considerable variation in the magnitude of response to ligation. Following ligation of the subclavian artery there was also a definite rise in the mean pressure within the internal mammary artery, which averaged 12.4 mm. Hg (Table II). The maximum rise in mean pressure following ligation of the subclavian artery was 16 mm. Hg, whereas the minimum rise was 7 mm. Hg, again revealing a variation in response to arterial ligation. The average rise in mean intra-arterial pressure in the internal mammary artery following ligation of the subclavian artery was greater by 1.4 mm. Hg than that following ligation of the internal mammary artery. Although there was a definite rise in the mean pressure in the proximal segments of the ligated internal mammary or subclavian arteries, there was a simultaneous rise of a similar magnitude in intra-arterial mean pressure at the other two sites of pressure measurement in the systemic arterial circulation in all 10 animals (Tables I and II).

TABLE III. MEAN INTRA-ARTERIAL PRESSURE RISE MEASURED SIMULTANEOUSLY FROM THE SUBCLAVIAN AND LEFT ANTERIOR DESCENDING CORONARY ARTERIES FOLLOWING LIGATION OF THE INTERNAL MAMMARY ARTERY

ANIMAL NUMBER	LIGATION OF INTERNAL MAMMARY ARTERY RISE IN MEAN PRESSURE (MM. Hg)	
	SUBCLAVIAN	LEFT ANTERIOR DESCENDING CORONARY
11.	10	9
12.	8	8
13.	9	10
14.	12	14
15.	8	6
Average	9.4	9.4

The findings in the animals of Group II (Tables III and IV) revealed an average rise in mean pressure in the subclavian arteries of 9.4 mm. Hg following internal mammary artery ligation. There was, however, an associated simultaneous rise in mean pressure of a similar magnitude in the left anterior descending coronary artery in all animals in response to ligation of the internal mammary artery. A similar simultaneous rise in systemic and coronary arterial mean pressure was recorded following subclavian artery ligation. The average rise in mean pressure recorded in the latter instance was 9.8 mm. Hg.

The findings in the animals of Group III (Table V) revealed that the fall in intra-arterial pressure in the distal segment of the ligated internal mammary persisted, in part, for a period of at least 5 weeks. Obvious variables would not allow an assessment of the duration of the rise in pressure in the proximal segment of the ligated internal mammary artery. The failure of the pressure in the distal segment of the ligated artery to return to levels near that in the proximal segment revealed a persistence of an increased pressure gradient between the proximal and distal segments of the ligated internal mammary artery.

Because of the difficulty of controlling a so-called "basal state" as well as other significant variables, it was felt that it would be extremely difficult, if not impossible, to determine the duration of the rise in pressure. Therefore, no attempt was made in these studies to evaluate the duration of the rise in pressure in response to the systemic arterial ligations performed.

A most interesting finding was the nature of the rise in pressure which occurred following the arterial ligations. Instead of the expected immediate maximum response it was noted that, while there was a definite immediate rise in pressure following arterial ligation, the maximum pressure response was not attained until from 6 to 10 beats had transpired. This type of pressure response was simultaneously recorded in both the systemic and coronary arterial systems and occurred consistently in all animals in Groups I and II.

TABLE IV. MEAN INTRA-ARTERIAL PRESSURE RISE MEASURED SIMULTANEOUSLY FROM THE SUBCLAVIAN AND LEFT ANTERIOR DESCENDING CORONARY ARTERIES FOLLOWING LIGATION OF THE SUBCLAVIAN ARTERY

ANIMAL NUMBER	LIGATION OF SUBCLAVIAN ARTERY RISE IN MEAN PRESSURE (MM. Hg)	
	SUBCLAVIAN	LEFT ANTERIOR DESCENDING CORONARY
11.	8	7
12.	8	8
13.	11	10
14.	14	15
15.	8	9
Average	9.8	9.8

TABLE V. SYSTOLIC ARTERIAL PRESSURE GRADIENTS BETWEEN PROXIMAL AND DISTAL INTERNAL MAMMARY ARTERY SEGMENTS, AT 2, 4, AND 5 WEEKS FOLLOWING INTERNAL MAMMARY ARTERY LIGATION

ANIMAL NUMBER	SYSTOLIC PRESSURE GRADIENTS (MM. Hg)		
	2 WEEKS	4 WEEKS	5 WEEKS
16.	16	20	22
17.	30	24	26
18.	18	26	20
19.	16	14	20
20.	24	21	18

DISCUSSION

In applying the acquired data to the first of the pressure responses necessary to substantiate the physiologic hypothesis under investigation, we find that there was, indeed, a definite rise in pressure in the proximal segment of the ligated

internal mammary artery as seen in the animals of Group I. Since the measured pressure rose, in spite of the decreased rate of flow through the internal mammary artery, and therefore the decreased Bernoulli effect, the actual hydrostatic pressure rose even more significantly than our recorded pressures indicate. Although the rise in pressure was a consistent response of a varying magnitude, it is obvious that an average rise in mean pressure of 11 mm. Hg cannot be construed as a profound alteration in pressure. Cognizant of the internal diameters of the vessel system under consideration (internal mammary-pericardiophrenic), we find it extremely difficult to ascribe a significant alteration in the volume flow per unit time to the average rises in mean pressure of the amplitudes recorded herein.

Holman's original thesis[6] that the high "end pressure" in a ligated parent artery would be transformed into "lateral pressure," which would be directed into its branch arteries, was also corroborated in the animals of Group I. Ligation of the parent subclavian artery resulted in a rise in pressure in the proximal segment of the subclavian artery, and a similar simultaneous response was recorded from the branch internal mammary artery. It is apparent that this finding would support the view that a rise in pressure in the parent internal mammary artery following ligation would be reflected in the branch pericardiophrenic artery.

Of more significance than the initial two responses, which in themselves might favor an increased flow, was the simultaneous rise in pressure noted in both the systemic and coronary arterial systems. It was immediately apparent that the rise in pressure was not a phenomenon localized to the internal mammary-pericardiophrenic system but was a generalized response occurring in both the systemic and coronary arterial circuits. The generalized response in the systemic circuit corroborated the studies of Taber and Marchiaro,[8] who noted consistent elevations of pressure in the subclavian arteries of dogs following bilateral internal mammary artery ligations. Glover's initial studies of pressure response,[2] however, did not reveal a generalized change in systemic pressure associated with internal mammary artery ligation.

Perhaps the most interesting finding in the study, and one which deserves further investigative amplification, was the nature of the pressure response to ligation wherein the maximum rise in pressure occurred only after from 6 to 10 beats had transpired. This suggested that the generalized rise in systemic and coronary pressure was, in part at least, a reflection of neural and/or humoral factors. The obvious increased resistance to flow secondary to arterial ligation was probably only of minor significance, with the major rise in pressure being due perhaps to the proposed neural and/or humoral factors. It is extremely dubious that the volume flow which passes through the internal mammary artery, by its interruption, would be responsible for a significant increase in resistance, which in turn might be reflected as a measurable generalized rise in pressure. If the latter is true, then the duration of effect of the neural and/or humoral factors should have definite, although variable, time limit.

We feel, then, that since, in this study, systemic and coronary arterial pressure responses to ligation of the internal mammary and/or subclavian arteries

tended to maintain pre-ligation pressure relationships, it is difficult, if not impossible, to establish a logical physiologic explanation for increased coronary flow on the basis of altered pressure gradients between arterial vessels subsequent to ligation of the internal mammary artery in canine animals. These findings have been corroborated in our laboratories by studies of cardiac output and coronary blood flow prior and subsequent to bilateral internal mammary artery ligation performed on fasting human subjects in a so-called "basal state."[9]

SUMMARY

Ligation of the internal mammary artery in canine subjects was found to have an associated consistent rise in pressure of a varying magnitude in the proximal segment. The rise in pressure in the proximal segment of the ligated artery was transmitted from the parent vessel to its branch segments. The evoked pressure response, however, was not localized to the internal mammary-pericardiophrenic system but was a simultaneous generalized response recorded in both the systemic and coronary arterial systems. The nature of the pressure response suggested that the generalized rise in systemic and coronary arterial pressure following ligation of the systemic artery was due in part to neural and/or humoral factors. The significance of the above findings was briefly discussed.

The authors wish to acknowledge the technical assistance of Mr. Marcus Ravnan.

REFERENCES

1. Battezzati, M., Tagliaferro, A., and DeMarchi, G.: Minerva med. **46**:1173, 1955.
2. Glover, R. P., Davila, J. C., Kyle, R. H., Beard, J. C., Trout, R. C., and Kitchell, J. R.: J. Thoracic Surg. **34**:661, 1957.
3. Glover, R. P.: J. Arkansas M. Soc. **54**:223, 1957.
4. Glover, R. P. Kitchell, J. R., Kyle, R. H., Davila, J. C., and Trout, R. G.: Dis. Chest **23**:637, 1958.
5. Kitchell, J. R., Glover, R. P., and Kyle, R. H.: Am. J. Cardiol. **1**:46, 1958.
6. Holman, E.: Surgery **26**:889, 1949.
7. Sabiston, D. C., Jr., and Blalock, A.: Surgery **43**:906, 1958.
8. Taber, R. E., and Marchiaro, T.: A.M.A. Arch. Surg. **76**:781, 1958.
9. Rowe, G. G., Maxwell, G. M., Castillo, C. A., Crumpton, C. W., Botham, R. J., and Young, W. P.: New England J. Med. (In press.)

The Extent of Reversibility of Myocardial ischemia in Dogs

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Myocardial infarction results in a detectable concentration of intracellular enzymes, such as serum glutamic oxaloacetic transaminase (S.G.O.T.), in the peripheral blood.[1] A prerequisite for the appearance of a significant elevation of this enzyme in the blood has been thought to be irreversible myocardial damage.[2,3] In fact, clinically, it is felt that if reversibility of myocardial injury is demonstrated electrocardiographically, then no significant elevation of the enzyme (S.G.O.T.) should be noted in the serum.

The purpose of this work was to study the reversibility of temporary myocardial injury by correlating certain biochemical, electrocardiographic, and pathologic observations.

MATERIAL AND METHODS

Twenty-nine mongrel dogs of both sexes were used. The animals were anesthetized with Nembutal (12 mg./lb.), and maintained with artificial respiration. The chest was opened and the pericardial space was entered. The circumflex branch of the left coronary artery was dissected free from the surrounding tissue, and an umbilical tape was placed 1.5 to 2 cm. distal to the bifurcation. The coronary sinus was catheterized with a No. 10 F. cardiac catheter through the left jugular vein. Heparin, 75 to 100 mg., was given to each animal. The time which elapsed between the opening of the chest and the collection of the "base-line" samples was 30 to 45 minutes. The circumflex branch of the left coronary artery was then occluded by previously placed umbilical tape. The ends of the tape were drawn through a small rubber vial cap, sufficiently tight to produce occlusion of the circumflex branch of the left coronary artery. Care was taken to prevent pinching or injury to the vessel wall.

Coronary venous samples were obtained as a free flow from the catheter in 7 dogs after 20 minutes of occlusion, and in 7 additional dogs after 40 minutes of occlusion. In some experiments the coronary sinus samples were obtained at 5-minute intervals during the initial 20 minutes of occlusion. After the specified period of occlusion the coronary artery was released in order to permit visible re-establishment of the circulation. Blood samples were taken at 20 and 40 minutes after release.

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In 8 dogs the coronary occlusion was maintained for 60 minutes, and samples were taken at this time and at 20 and 40 minutes after re-establishment of coronary flow.

To observe the effects of surgery per se upon the level of serum glutamic oxaloacetic transaminase, 7 dogs were subjected to the above-described procedures without coronary ligation. "Base-line" coronary sinus samples were followed by samples taken at 20-minute intervals during a 60-minute period.

The myocardium of 7 animals which were permitted to survive temporary coronary occlusion were examined histologically. Protamine sulfate (100 mg., intravenously) and penicillin-streptomycin (intrathoracically and intramuscularly) were administered to these animals in the immediate postoperative period. The antibiotics were continued daily.

Serum glutamic oxaloacetic transaminase activity was measured in the Beckman DU spectrophotometer by standard techniques,[4] and serum potassium was determined by flame photometry.

Electrocardiograms with Lead AVF were obtained throughout the course of each experiment.

RESULTS

The mean S.G.O.T. activity in the preocclusion "base-line" samples of the 14 dogs subjected to coronary ligation was 25.9 ± 9.4 units (Table I). S.G.O.T. values obtained at 5, 10, and 15 minutes postocclusion were not elevated. However, at 20 and 40 minutes following occlusion, the transaminase activity of the coronary sinus blood was significantly increased. These elevated values were not altered by 20 or 40 minutes of re-established coronary flow.

In 8 dogs in which the coronary artery was occluded for 60 minutes, there was a progressive rise in the concentration of serum enzyme during the 40 minutes following re-establishment of the coronary circulation (Table I).

TABLE I. RELEASE OF TISSUE ENZYMES (G.O.T.) FOLLOWING TEMPORARY OCCLUSION OF CORONARY ARTERY (UNITS/MIN./ML.)

PREOCCLUSION	POSTOCCLUSION			POSTRELEASE	
	20 MIN.	40 MIN.	60 MIN.	20 MIN.	40 MIN.
25.9* ± 9.4 (14)	39.0** ±15.3 (13)	56.5** ±11.9 (7)		41.0** ±11.6 (12)	48.0** ±11.4 (6)
34.4 ±12.6 (8)			51.0** ±14.1 (8)	57.0** ±15.5 (6)	72.0** ±16.8 (6)

*Mean and standard deviation of the mean.
**P < 0.05 or 0.01 as compared to the preocclusion value.
Number of animals are indicated in parentheses.

The mean "base-line" value of S.G.O.T. in the 7 sham-operated dogs was 28.0 ± 9.2 units/min./ml., and this value did not significantly change at 20, 40, or 60 minutes postsurgery.

No significant increase occurred in the concentration of potassium in the coronary sinus blood after 2, 5, 8, 10, or 20 minutes of occlusion.

Electrocardiographic evidence of myocardial injury was observed in all of the dogs with coronary occlusion, and resembled the changes previously described.[5-7] These changes consisted of S-T segment elevations and inversion or formation of giant T waves. All of the electrocardiographic manifestations of injury appeared within the initial 2 to 5 minutes of myocardial ischemia. In 10 of the 22 dogs which were subjected to coronary occlusion, partial reversion of the electrocardiographic abnormalities toward the control or base-line record occurred within minutes following the release of the coronary ligature. Nine dogs had a gradual regression of the ECG abnormalities over a 20-minute period after release.

In 2 dogs, ST-T changes persisted for the 80 minutes' duration of the post-occlusion period. In 2 other dogs, prominent Q waves developed during the period of coronary ligation and remained during the 40 minutes' re-established coronary circulation. Prolongation of intraventricular conduction and a reduction in the amplitude of the R wave with the appearance of a Q wave, which were rarely seen, disappeared upon the re-establishment of the coronary circulation.

When occlusion of the coronary vessel was maintained for 60 minutes, the electrocardiograms of 2 dogs gradually returned toward the control pattern. Six of the 8 animals had ECG evidence of irreversible myocardial damage.

No consistent alteration of femoral arterial pressure or pulse rate was noted during the procedure.

Histologic examination was made of 11 hearts sectioned serially through the area of the myocardium supplied by the circumflex coronary artery. Four of the hearts were removed and fixed in formaldehyde upon completion of the experiment. Seven animals were sacrificed from 2 to 6 days after the induction of myocardial injury. Eight of the 11 animals had shown elevated transaminase levels in the coronary sinus blood. All had demonstrated electrocardiographic evidence of myocardial injury. However, in the heart of only one animal was there histologic evidence of recent myocardial infarction in the area supplied by the circumflex branch of the left coronary artery. Involvement included the subendocardial region of the posterolateral wall and the posterior papillary muscle. This animal had been subjected to 40 minutes of coronary occlusion, as had 3 other animals of this group. The coronaries of the remaining 7 animals had been occluded for 20 minutes. The extent of transaminase elevation in the animal with histologic evidence of myocardial damage was not striking.

Histologic examination was not made of the 8 hearts from dogs subjected to 60 minutes of coronary occlusion.

DISCUSSION

Temporary myocardial injury may result in the release of intracellular enzymes and in alterations in repolarization of the heart. These two measurable responses to injury apparently develop at different rates. Furthermore, the significant elevation of intracellular enzyme, such as G.O.T., in the serum does not necessarily indicate irreversible cellular damage.

Repolarization of myocardial cells is poorly understood but is presumably related to active metabolic processes.[8] These processes are affected by the surrounding ionic milieu. The effect of hypoxia upon repolarization was apparent in the dog subjected to temporary coronary ligation, as evidenced by the changes in this phenomenon. Yet, while coronary occlusion was maintained, evidence of altered repolarization began to wane, being related probably to the rich collateral coronary circulation of the dog. The repolarization changes disappeared after the reinstitution of coronary flow in almost all of the hearts subjected to myocardial ischemia of 20 or 40 minutes' duration. There was not a consistent correlation between the muscular damage produced by a longer period of ischemia (60 minutes) and the electrocardiographic findings. In some instances the electrocardiogram failed to show irreversible changes, whereas the enzyme concentration continued to increase and myocardial ischemia was visibly apparent.

T-wave inversions do not necessarily represent early evidence of ischemia in dogs. Thoracotomy may induce this nonspecific change in the ECG, or the T wave may be inverted or biphasic in dogs. The decrease in the height of the R wave and simultaneous development of significant Q waves observed in some instances is probably related to vectorial changes following the acute ischemia. The abnormal movement of intracellular substances through an ischemic membrane implies some disturbance in membrane integrity. Release of potassium from severely ischemic cardiac tissue with ventricular dysrhythmias has been documented[9] and is suggestive of an altered permeability of the membrane as an early manifestation of injury (10 minutes).[10] Passage of larger molecules, such as enzymes, through a membrane is more difficult to understand. Either large spaces must develop in the membrane to permit enzyme escape or the released enzyme may result from disturbed metabolic processes of the cell membrane.[11] In either event, ischemia must be present for a protracted period in order to cause membrane damage and to permit the release of tissue enzymes. Electrical alterations of the membrane caused by ischemia are more immediate and labile than the alterations caused in the metabolic processes of the membrane. The promptness with which the electrical alterations occur in hypoxia may have a closer temporal relationship with the passage of intracellular potassium into the extracellular spaces than with the release of the large protein molecule of an enzyme. Failure to find any significant change in the concentration of potassium in the coronary venous blood in these experiments may be related to the dilution of released intracellular cations by the large volume of extracellular fluid or to the persistence of normal sinus rhythm.

The fate of cellular enzymes, such as glutamic oxaloacetic transaminase, released from the cell has not been clearly defined. The persistently elevated concentration of coronary sinus G.O.T. after the removal of the 40-minute occlusion is probably related to a generalized increase in the enzyme level of the circulating blood. When cellular enzymes continue to be released after reinstitution of coronary flow, as in the 60-minute occlusion experiments, the transaminase level of the coronary venous blood increases progressively.

Gould[12] records histologic observations of early myocardial ischemic changes characterized by cloudy swelling, edema, and congestion as early as 30 minutes

after permanent occlusion. Blumgart and associates[5] noted persistent myocardial lesions in dogs in which temporary coronary occlusion had been induced for 25 to 45 minutes. Electron microscopic studies in rats have shown significant protoplasmic changes after one-hour ligation of the coronary artery.[13] In our study, these early histologic changes must have been readily reversible, since re-establishment of coronary circulation for 40 to 60 minutes caused an apparent reversion to normal of the early histologic evidence of muscle injury in 4 dogs. That longer periods of cellular anoxia (60 minutes) may produce permanent damage is suggested by the continued release of cellular enzymes in coronary sinus blood.

Extrapolation of this data to patients with occlusive coronary artery disease must be done with caution, for differences exist between man and dog in collateral circulation. Furthermore, in the dog experiments heparin was administered during the course of muscle injury.

SUMMARY

1. Electrocardiographic, biochemical, and pathologic indications of temporary myocardial ischemia vary in the rate of appearance and reversibility.

2. Electrocardiographic changes were consistently observed immediately following occlusion of the coronary artery, and these changes regressed toward the base-line record if coronary flow was reinstituted within 40 minutes.

3. A significant rise in glutamic oxaloacetic transaminase was observed in the coronary sinus blood after 20 minutes of occlusion. An elevation of the enzyme concentration in the serum, even for a period of 40 minutes, does not necessarily indicate irreversible cellular damage.

4. Tissue injury which was readily reversible occurred after 40 minutes of coronary occlusion. Sixty minutes of sustained tissue anoxia appears to be the critical period beyond which irreversible damage occurs.

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REFERENCES

1. LaDue, J. S., Wroblewski, F., and Karmen, A.: Serum Glutamic Oxaloacetic Transaminase Activity in Human Acute Transmural Myocardial Infarction, Science **120**:497, 1954.
2. LaDue, J. S., and Wroblewski, F.: Significance of SGO-Transaminase Activity Following Acute Myocardial Infarction, Circulation **11**:871, 1955.
3. Nydick, I., Wroblewski, F., and LaDue, J. S.: Evidence for Increased Serum Glutamic Oxaloacetic Transaminase (SGO-T) Activity Following Graded Myocardial Infarcts in Dogs, Circulation **12**:161, 1955.
4. Karmen, A., Wroblewski, F., and LaDue, J. S.: Transaminase Activity in Human Blood, J. Clin. Invest. **34**:126, 1955.
5. Blumgart, H. L., Gilligan, D. R., and Schlesinger, M. J.: Experimental Studies on Effect of Temporary Occlusion of Coronary Arteries: Production of Myocardial Infarction, Am. Heart J. **22**:374, 1941.
6. Bayley, R. H., LaDue, J. S. and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, Am. Heart J. **27**:164, 1944.
7. Nydick, I., Ruegsegger, P., Wroblewski, F., and LaDue, J. S.: Variations in Serum Glutamic Oxaloacetic Transaminase Activity in Experimental and Clinical Coronary Insufficiency, Pericarditis, and Pulmonary Infarction, Circulation **15**:324, 1957.

8. Weidmann, S.: Transport of Ions Across Cardiac Membranes. *In* Metabolic Aspects of Transport Across Cell Membranes, edited by Q. R. Murphy, Madison, 1957, Univ. of Wisconsin Press, p. 115.
9. Harris, A. S., Bisteni, S., Russell, R. A., Brigham, J. C., and Firestone, J. E.: Excitatory Factors in Ventricular Tachycardia Resulting From Myocardial Ischemia. Potassium a Major Excitant, Science **119**:200, 1954.
10. Harris, A. S., Toth, S. A., and Hoey, T. E.: Arrhythmic and Antiarrhythmic Effects of Sodium, Potassium, and Calcium Salts and of Glucose Injected Into Coronary Arteries of Infarcted and Normal Hearts, Circulation Res. **6**:570, 1958.
11. Wilson, I. B., and Nachmansohn, D.: The Generation of Bioelectric Potentials. *In* Ion Transport Across Membranes, edited by H. T. Clarke, New York, 1954, Academic Press, p. 39.
12. Gould, S. E.: Pathology of the Heart, Springfield, Ill., 1953, Charles C Thomas, p. 592.
13. Bryant, R. E., Thomas, W. A., and O'Neal, R. M.: An Electron Microscopic Study of Myocardial Ischemia in the Rat, Circulation Res. **6**:699, 1958.

The Simultaneous Estimation of Right and Left Ventricular Outputs Applied to a Study of the Bronchial Circulation in Dogs

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Agreement exists among anatomists with respect to the origin and distribution of the bronchial arteries. Continuity may be found between the bronchial capillary net and the alveolar capillaries perfused by the pulmonary artery, and arterial bronchopulmonary anastomoses have been described by most observers,[1] although their actual existence in the normal subject is still uncertain.[2] Anatomic evidence suggests that both the azygos and the pulmonary venous systems participate in the bronchial venous drainage.[3,4] Measurements of the normal bronchial blood flow in man are not available, but in the dog it has been estimated to comprise approximately 0.5 to 1.5 per cent of the left ventricular output.[5-7]

Greatly expanded and functionally significant postcapillary anastomoses develop in the dog following permanent ligation of the pulmonary veins of one lung.[8] The bronchopulmonary venous communications are also much enlarged in certain types of chronic lung disease[9] and in patients with mitral stenosis.[4,10] No data have been reported of estimates of the collateral venous flow in man. Bronchopulmonary arterial collateral circulation can be induced in the dog by ligation of one pulmonary artery.[11] Similarly, precapillary anastomoses may develop in man if one pulmonary artery is congenitally absent or has been obliterated.[12,13] Extensive bronchopulmonary communications are found also in certain types of congenital heart disease and in chronic pulmonary diseases. Quantitation of the blood flow through these communications has been attempted both in man and in dogs by application of the Fick principle[11,14] and by using mixing formulas[15] or elaborate supplementary measurements.[16] All of these studies suggest that an appreciable fraction of the left ventricular output returns through these channels to the left atrium.

An alternative approach to the measurement of the bronchial collateral flow is offered by simultaneous determination of right and left ventricular output.

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Dilution curves obtained from the pulmonary artery after injection of an indicator close to the right atrium have been found to give an accurate measure of the right ventricular output.[17] The present studies are concerned with simultaneous independent estimates of right and left ventricular output by the indicator dilution method. Simultaneous direct recording of dye dilution curves from the pulmonary and the femoral arteries have given essentially congruent results.[18,19] It was our purpose to validate the method with measurements in normal dogs, and further, to apply it to animals in which precapillary bronchopulmonary anastomoses had been induced by surgical interference. Glass model experiments were performed to control the technique used. Clinical studies will be presented in a subsequent paper.

Although the bronchopulmonary anastomoses may not be the only communication between the pulmonary and the systemic circulation, for the purpose of this presentation it is assumed that, in the steady state and in absence of other known shunts, an excess in left over right ventricular output is a measure of the bronchopulmonary circulation. Fig. 1 gives a diagrammatic representation of these components of the left ventricular flow. The bronchial venous blood returning to the right atrium through the azygos system is not specifically included.

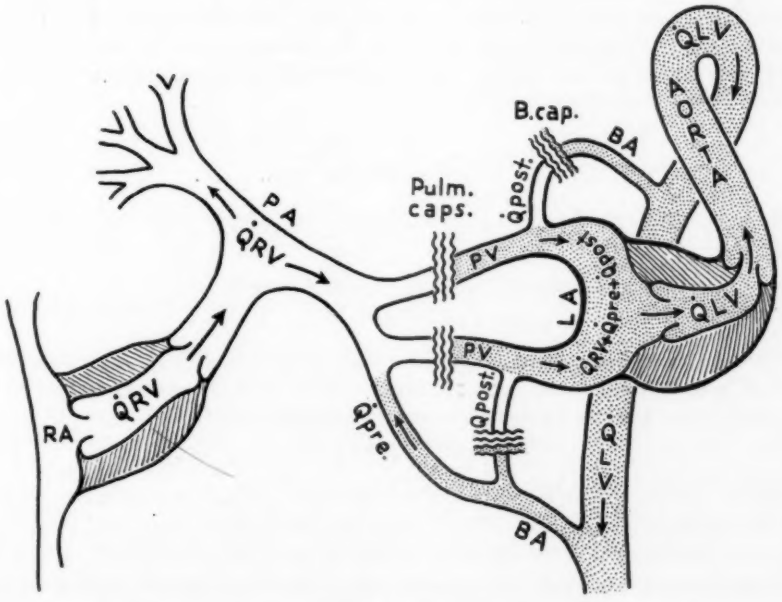

Fig. 1.—Diagram showing components of left ventricular output. ***RA:*** **Right atrium.** ***PA:*** **Pulmonary artery.** ***LA:*** **Left atrium.** ***BA:*** **Bronchial arteries.** ***$\dot{Q}RV$:*** **Right ventricular output.** ***$\dot{Q}pre$:*** **Precapillary anastomosis, flow.** ***$\dot{Q}post$:*** **Postcapillary anastomosis, flow.** ***B. cap.:*** **Bronchial capillaries.** ***Pulm. caps.:*** **Pulmonary capillaries. Vessels normally containing venous blood are white, and those normally containing arterial blood are shaded.**

METHODS

Radioiodinated human serum albumin (RISA) was chosen as the indicator. At the outset, problems arose in measuring the exact amount of RISA delivered into the circulation and in obtaining reliable curves with a sharp ascent and an adequate number of points on the downslope

before recirculation. These problems were solved by measuring the weight rather than the volume of the indicator injected, by carefully recovering the isotope retained on the wall of the injection catheter, and by injecting the indicator close to the right atrium. Mongrel dogs of medium to large size were used. The animals were anesthetized with pentobarbital sodium (30 mg./Kg.). Spontaneous respiration was maintained through a tracheal cannula.

A size 9 cardiac catheter was guided under fluoroscopy into the main pulmonary artery via the superficial jugular vein, and a small polyethylene catheter (P190) was placed into the femoral artery. The dead space of the cardiac catheter and attachment was 2.1 ml., and that of the femoral artery tubing was 1.8 ml. A second cardiac catheter, size 8, was threaded into the femoral vein and advanced to a point just proximal to the right atrium. A three-way stopcock was attached to this catheter, and a syringe containing 10 ml. of saline placed in line with the catheter. A weighed tuberculin syringe containing a known amount of isotope was attached to the right-angle limb of the stopcock. The isotope was displaced into the catheter, which had a capacity of at least twice that of the volume to be injected. The stopcock was turned in line with the saline syringe, and at a signal the indicator was washed into the circulation as a bolus with about 15 times its volume of saline. At the end of the injection the tuberculin syringe was removed and reweighed. The injection catheter with the stopcock attached was removed and washed out with 250 ml. of saline. The activity of the washout was measured.

Beginning simultaneously with the injection, samples of about 1.1 ml. were withdrawn from the pulmonary and femoral arterial catheters by two Cornwall spring-loaded syringes at one-second intervals and delivered into each of the 29 tubes of two synchronously revolving fractional collectors. The sample in each tube was corrected to volume by adding a measured amount of saline, and counted for 2 minutes in a scintillation well-counter. As a rule, no activity was noted in the first two pulmonary arterial samples and in the first 8 femoral arterial samples. Rectilinear plots were constructed to compare the shape of the two simultaneous curves. Flows were calculated from the two semilogarithmic plots with extrapolation of the downslope to 0.1 per cent of peak value by the Stewart-Hamilton equation:

$$F = \frac{\text{"I"} \times 60}{\text{Area under the curve}}$$

where F is the rate of blood flow and "I" is the amount of isotope injected. "I" was found by the equation:

$$\text{"I"} = \frac{\text{Counts in standard} \times \text{Weight of dose injected}}{\text{Weight of standard}} - \text{Counts in washout.}$$

The difference between left and right ventricular outputs was taken as an estimate of the blood flowing through bronchopulmonary communications; because it is expected normally that some bronchial arterial blood returns to the left atrium, the equation:

$$\dot{Q}_{LV} - \dot{Q}_{RV} = \dot{Q}_{BA}$$

was used, where: $\dot{Q}_{LV}$ = left ventricular blood flow, L./minute.
$\dot{Q}_{RV}$ = right ventricular blood flow, L./minute.
$\dot{Q}_{BA}$ = bronchopulmonary collateral blood flow, L./minute.

Within 5 minutes a cardiac output was determined by the Fick method, measuring the oxygen uptake for 5 minutes in a closed-circuit, oxygen-filled spirometer with a CO_2 absorber, and sampling arterial and venous blood from the femoral and main pulmonary arteries, in the usual manner. In one especially prepared animal, bronchial flow was estimated by the method of Bloomer and associates.[11]

The validity of the method was demonstrated in two glass model experiments. To test the accuracy of recovery of the indicator injected, a weighed amount of isotope was injected into a 5-liter tank containing 3 liters of blood and 2 liters of saline constantly agitated. The content of the tank was thoroughly mixed before sampling. The numerator "I" of the formula,

$$V = \frac{\text{"I"}}{\text{average concentration/ml.}},$$

was determined as above. The activity recovered from the catheter in the washout after injection equalled 9.3 per cent. In this and in the second model experiment, samples of about 1.1 ml. were withdrawn as in the in vivo studies described above. The capacities of the two syringes were deliberately made unequal in this model experiment in order to determine the effect, if any, of volume differences on the counts in each aliquot after correction to constant volume. Each tube was counted for 2 minutes in a scintillation well-counter, and the two sets of 29 tube counts, after background subtraction, were compared with the calculated value. Although a difference existed between the two series, the standard error in each was not in excess of 1 per cent of the theoretical value. Calculation of the value in the tank from the mean concentration in the 58 samples yielded a value within 0.6 per cent of the known volume.

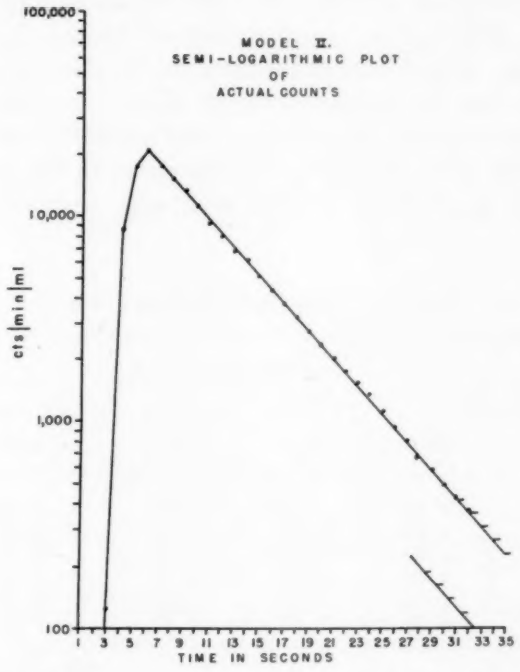

Fig. 2.—Curve obtained from model (*cts/min/ml* = counts per minute per milliliter).

To assess the accuracy of the present method of rapid intermittent sampling for the construction of an isotope dilution curve from which precise flows could be calculated, a second model experiment was set up. In this experiment a constant and accurately measured flow of saline was maintained by pressure; a mixing chamber of 300 ml., in which the fluid was maintained in constant agitation, was interposed between inflow and outflow tubing. Recirculation did not apply. The isotope was weighed and injected in the usual manner proximal to the mixing chamber. Simultaneous sampling was performed, distal to the mixing chamber, through the femoral and cardiac catheters. Since the numerator "I" could be accurately measured, it became possible to check the denominator of the formula. Flow so calculated was within 1.05 per cent of the known values. Fig. 2 shows one of the semilogarithmic plots obtained. Since the dead space of the sampling catheters was 2.1 ml. and 1.8 ml., respectively, the activity in the aliquot delivered was approximately 2 seconds behind that of the sampling site. This factor should be taken into consideration in assessing circulation times, but does not influence the construction of the curves for flow calculation, as long as the volume of the individual samples is adequate. If samples of less than 0.6 ml. were delivered, contamination of consecutive samples in the catheter's dead space would occur, causing a stepwise distortion of the curve and impairing its angle of descent. During the in vivo studies, runs in which three or more samples of less than 0.6 ml. were drawn during the first 15 seconds were discarded.

RESULTS

The results of this study are subdivided into three sections: Section 1, comprising measurements of right and left ventricular output in 6 normal dogs; Section 2, concerning serial studies on one dog in which an artificial shunt between the systemic circulation and the pulmonary artery had been established; and, Section 3, including 6 dogs with permanent occlusion of the left pulmonary artery.

Section 1.—The results of studies in 6 normal dogs are summarized in Table I. The mean difference between the two ventricular outputs in this group of normal dogs shows an excess of left over right and is significant statistically at the P = 0.05 level, although one must entertain doubts about the validity of these small differences. Fig. 3 is an example of the rectilinear and semilogarithmic plots from Dog 609, and is representative of normal curves. The peak of the femoral arterial curve is lower than that of the pulmonary arterial curve, indicating further dilution of the indicator on its course to the aorta. The semilogarithmic plots show good linear downslopes, with insignificant deviations of single points.

TABLE I. STUDIES IN NORMAL DOGS

DOG NUMBER	WEIGHT (LBS.)	BLOOD FLOW (L./MIN.)				$\dot{Q}_{BA}$ AS PER CENT OF $\dot{Q}_{LV}$ (% DIFFERENCE)
		FICK	$\dot{Q}_{RV}$	$\dot{Q}_{LV}$	$\dot{Q}_{BA}$	
639	28.0	1.59	1.49	1.66	0.17	10.2
608	30.5	1.29	1.42	1.44	0.02	1.4
609	33.0	1.75	2.28	2.27	−0.01	−0.4
581	40.0	1.46	1.41	1.51	0.10	6.6
A. VA	31.0	2.60	2.97	3.02	0.05	1.7
668	23.0	2.31	1.51	1.57	0.06	3.8
					Mean = 0.065 S.D. = 0.049 "t" = 2.51 P < 0.05	

Section 2.—The studies in this section concern one dog with a direct end-to-end anastomosis between the left subclavian and the distal left pulmonary arteries. Three studies were carried out at intervals of about 2 months, and in the last study the difference between the outputs from the two ventricles was compared with a flow determination using the technique of Bloomer and associates.[11] Table II summarizes the results. The initial difference between $\dot{Q}_{LV}$ and $\dot{Q}_{RV}$ diminished 4 months after the operation, presumably as a result of partial stenosis of the anastomosis. On the rectilinear plot of the femoral arterial curve (Fig. 4) a distinct step in the downslope is apparent and differs from the normal pattern. This alteration in slope results from the rapid recirculation of indicator through the anastomosis.

Section 3.—Table III presents the measurements in a group of 6 dogs with permanent occlusion of the left pulmonary artery. All blood flow through the

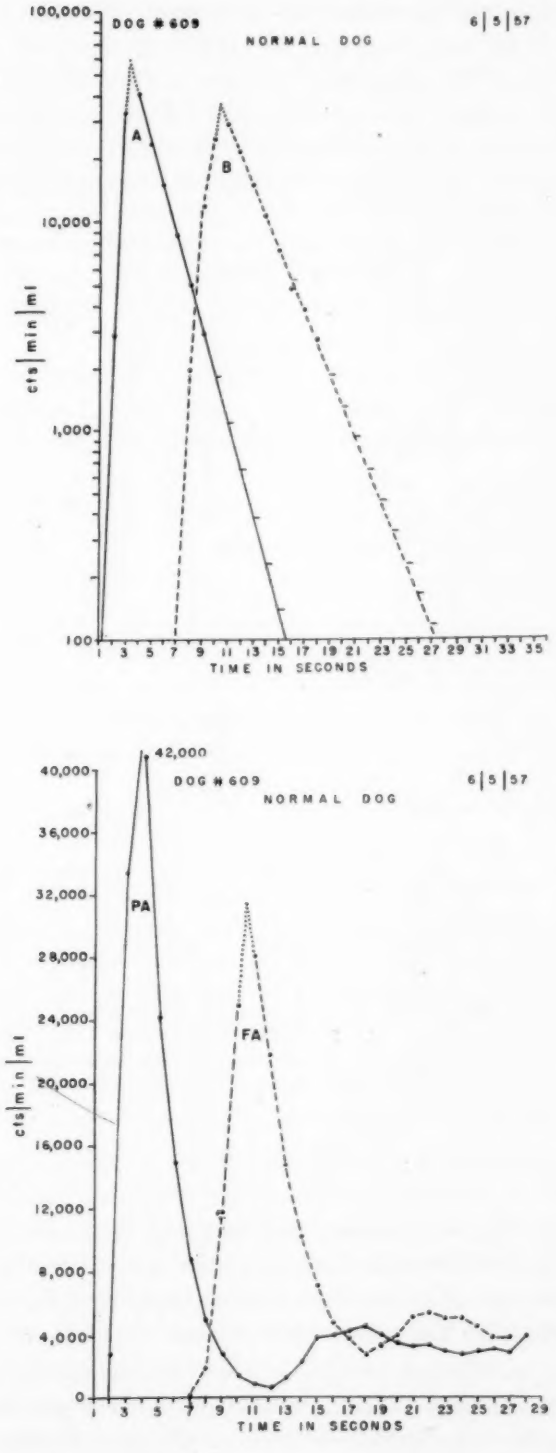

Fig. 3.—Curves obtained from a normal dog. *Top,* **Semilogarithmic.** *Bottom,* **Rectilinear.** ***A*** **and** ***PA:*** **Pulmonary arterial curves.** ***B*** **and** ***FA:*** **Femoral arterial curves.** ***cts/min/ml*** **= counts per minute per milliliter.**

left lung in these animals is presumably the result of extensive precapillary anastomoses between the bronchial and distal left pulmonary arteries. In Dogs 596 and 597, three sets of measurements over a number of months show a distinct increase in flow over the initial figures. With the exception of the study in Dog 583 and the first study in Dog 597, all values for $\dot{Q}_{BA}$ exceed by a very large margin the mean figure calculated for the normal series.

TABLE II. STUDIES IN A DOG WITH LEFT SUBCLAVIAN TO LEFT PULMONARY ARTERY END-TO-END ANASTOMOSIS (DOG NO. 606)

MONTHS AFTER OPERATION	BLOOD FLOW (L./MIN.)				$\dot{Q}$ SHUNT AS PER CENT OF $\dot{Q}_{LV}$ (% DIFFERENCE)
	FICK	$\dot{Q}_{RV}$	$\dot{Q}_{LV}$	$\dot{Q}$ SHUNT	
2	2.49	2.64	3.79	1.15	30.3
4	1.98	2.29	2.83	0.54	19.1
6	2.28	2.10	2.68	0.58	21.6
6	Using the Bloomer Technique			0.78	

TABLE III. STUDIES ON DOGS WITH PERMANENT OCCLUSION OF LEFT MAIN PULMONARY ARTERY

DOG NUMBER	TIME AFTER LIGATION (MONTHS)	BLOOD FLOW (L./MIN.)				$\dot{Q}_{BA}$ AS PER CENT OF $\dot{Q}_{LV}$
		FICK	$\dot{Q}_{RV}$	$\dot{Q}_{LV}$	$\dot{Q}_{BA}$	
583	6	2.06	3.56	3.59	0.03	0.84
587	9	2.55	2.19	2.68	0.49	18.3
595	9	1.52	1.21	1.48	0.27	18.2
596	2.5	1.062	2.71	2.92	0.21	7.2
	8	2.228	1.83	2.51	0.68	27.1
	9	1.923	1.81	2.29	0.48	21.0
590	8	2.35	1.72	1.96	0.24	12.2
597	3	2.60	2.97	3.03	0.05	1.7
	8	3.983	3.13	3.97	0.84	21.2
	10	4.291	4.47	5.37	0.90	16.8

DISCUSSION

The present studies have shown that in a well-controlled model the injecting and sampling technique described can account for all but a negligible amount of the injected isotope. Curves drawn from controlled flow rate model experiments agree closely with the known flow rates.

It was not expected that the present method would be sensitive enough to give an accurate estimate of the bronchopulmonary collateral blood flow in normal dogs. Rather, it was the purpose of the first series of measurements to test the congruity of simultaneous right and left ventricular output. The differences between the two measurements are, in fact, within the chance variations of the indicator dilution method. Nevertheless, in 5 out of 6 animals the left

ventricular output is higher than the right. On a priori grounds this should be expected, since some of the bronchial blood is returned to the left heart via the bronchial venules draining into the pulmonary veins. A small amount of indicator is withdrawn from the pulmonary artery before the blood carrying the indicator is further diluted to form the curve obtaining in the femoral artery, but the error introduced appears negligible. Since we have not detected technical errors in our gas analyses, and since the indicator dilution curves from the pulmonary and femoral arteries are in close agreement, only an unstable circulation and nonsimultaneous sampling for the RISA and for the oxygen uptake and blood oxygen determinations can be offered as an interpretation of the wide

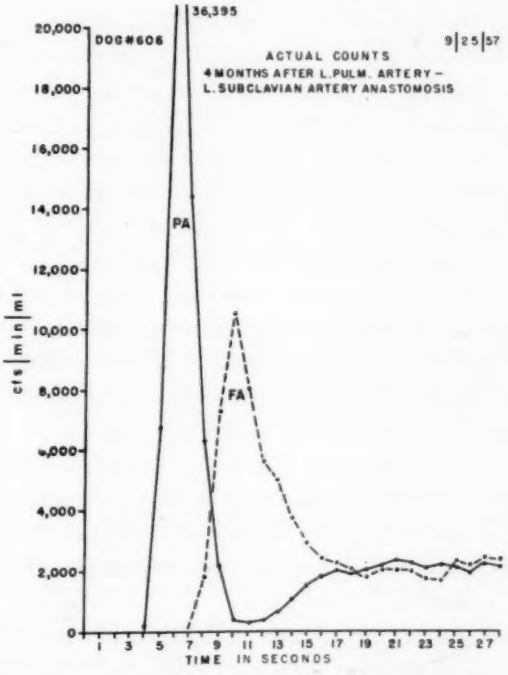

Fig. 4.—Curves from a dog 4 months after a subclavian-pulmonary artery anastomosis was created. ***PA:*** **Pulmonary arterial curve.** ***FA:*** **Femoral arterial curve.** ***cts/min/ml*** **= counts per minute per milliliter.**

difference noted in 2 normal dogs between the Fick and the indicator dilution methods. We have used Dog 606 (subclavian to pulmonary artery anastomosis) as a simplified living model of the arterial bronchopulmonary collateral circulation known to develop after ligation of the pulmonary artery. In this preparation the left ventricular work was increased; the amount of arterial blood recirculating to the left heart could readily be measured directly; and no stimulus to the formation of new collateral channels was introduced, nor are they known to develop. As expected, the estimated flow of the right ventricle is in agreement with the flow calculated by the Fick equation. The difference of 25 per cent between the indicator dilution technique and the method of Bloomer and associates is not excessive in view of the potential errors of this application of the Fick principle.[13] The magnitude of the difference between right and left ventricular output in

the dogs reported in Table III is in agreement with that noted in Dog 606 and with data obtained by others,[11] except in two measurements. Particularly with reference to Dog 597, the variable results in serial measurements suggest wide fluctuations in flow through these channels. Possibly, the abnormal communications had not developed fully at the time of the first measurement.

A definition of respective ventricular outputs becomes necessary when measuring blood flow in the presence of intracardiac or bronchopulmonary shunts. The usual Fick equation may not be applicable here, because the blood and respiratory gas samples are collected at three different sites when intervening shunts may make the blood passing through such sites nonhomogeneous. In the normal subject the Fick equation comprises the bronchial venous blood returning to the left ventricle via the pulmonary veins only in so far as this systemic venous blood affects the denominator by depressing the oxygen saturation of the arterial sample. In diseases causing enlargement of bronchial arteries,[16,20-22] the bronchopulmonary venous drainage probably also increases, further reducing the arterial oxygen saturation. The effect of expanded or more complex anastomoses[9,23] would depend on the direction of flow. When the arterial saturation is normal, the Fick method does not account for bronchial arterial flow diverted into the pulmonary arteries through precapillary anastomoses. In the presence of widespread precapillary communications, however, the result of the Fick method would vary according to the site in the pulmonary artery from which the venous sample is drawn. Evidence is available to indicate that retrograde flow from bronchial arterial anastomoses may increase the oxygen content of blood samples drawn from the main divisions of the pulmonary arteries, as compared with the mixed venous blood obtained from the right ventricle.[2,15,24,25] If the collateral flow observed in the diseased state occurs through an expansion of channels available also in the normal state, however difficult it may be to quantitate flow, these channels may constitute a sort of sluice mechanism between the pulmonary and the systemic circulation.

In the dog experiments reported in Table III the left ventricular output measured by the femoral arterial indicator dilution curve should be higher than the value calculated by the Fick equation. We have found higher results in seven determinations, and in only one was the indicator dilution curve value lower than the Fick value. The results of the pulmonary arterial indicator dilution (right ventricular output) and of the Fick methods should be equal except for that portion of the bronchial circulation returning via pulmonary veins which influences the Fick method but not the dilution curve. We have found wide variations in both directions. Such discrepancies between the Fick and the indicator dilution methods have been obtained by others,[27] and are ascribed to nonsteady blood flow and variable arteriovenous oxygen differences during the time in which the air and blood samples are collected. In our dogs these differences could be augmented by variations of quantity and direction of the collateral flow. Further studies are needed to define the mechanisms and to quantitate the probable range of these variations in specific situations. Lacking such information, the Fick method may not be a good reference method for the situations obtaining in the present experiments.

SUMMARY

The existence of an arterial blood supply to the lungs through the bronchial arteries, and the partial drainage of this blood into the pulmonary veins requires the output from the left ventricle to exceed that from the right ventricle by the amount of bronchial blood entering the pulmonary veins. The difference between the outputs of the ventricles of the heart is, therefore, an indirect measure of the systemic arterial blood flow to the lesser circulation in the absence of other obvious arteriovenous anomalies.

A method for the simultaneous determination of the outputs from both ventricles, using radioactive iodinated serum albumin dilution curves, has been described, as have experiments testing the method by means of models. In 5 out of 6 normal dogs the left ventricular output exceeded that of the right by a mean value of 67 ml./min. Very much larger differences were observed in a dog with an artificial end-to-end anastomosis between the left subclavian and left pulmonary arteries. In 8 out of 10 observations in dogs with permanent ligation of one pulmonary artery, values far in excess of the normal difference between the outputs of the two ventricles were found. This is consistent with the concept of an enlarged bronchial arterial system. Some of the implications of this study have been discussed.

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REFERENCES

1. Halmagyi, D. F. J.: Die klinische Physiologie des kleinen Kreislauf, Jena, 1957, Gustav Fischer Verlag.
2. Liebow, A. A., Hales, M. R., Harrison, W., Bloomer, W., and Lindskog, G. E.: The Genesis and Functional Implications of Collateral Circulation of the Lungs, Yale J. Biol. & Med. **22**:637, 1950.
3. Zuckerkandl, E.: Über die Anastomosen de Venae pulmonales mit den Bronchialvenen und mit dem mediastinalen Venennetze, Sitzungsb. d.k. Akad. d. Wissensch. Wien, Abt. 3, **84**:110, 1882.
4. Marchand, P., Gilroy, J. C., and Wilson, V. M.: An Anatomical Study of the Bronchial Vascular System and Its Variations in Disease, Thorax **5**:207, 1950.
5. Bruner, H. D., and Schmidt, C. F.: Blood Flow in the Bronchial Artery of the Anesthetized Dog, Am. J. Physiol. **148**:648, 1947.
6. Daly, M. DeB., Aviado, D. M., and Lee, C. Y.: The Contribution of the Venous Admixture in Pulmonary Venous Blood, 19th International Physiological Congress, Montreal, 1953, p. 298.
7. Salisbury, P. F., Weil, P., and State, D.: Factors Influencing Collateral Blood Flow to the Dog's Lung, Circulation Res. **5**:303, 1957.
8. Hurwitz, A., Calabresi, M., Cooke, R. W., and Liebow, A. A.: An Experimental Study of the Venous Collateral Circulation of the Lung, Am. J. Path. **30**:1085, 1954; and J. Thoracic Surg. **28**:241, 1954.
9. Liebow, A. A.: The Bronchopulmonary Venous Collateral Circulation, With Special Reference to Emphysema, Am. J. Path. **29**:251, 1953.
10. Ferguson, F. C., Kobilak, R. E., and Deitrik, J. E.: Varices of the Bronchial Veins as a Source of Hemoptysis in Mitral Stenosis, AM. HEART J. **28**:445, 1944.
11. Bloomer, W. E., Harrison, W., Lindskog, G. E., and Liebow, A. A.: Respiratory Function and Blood Flow in the Bronchial Artery After Ligation of the Pulmonary Artery, Am. J. Physiol. **157**:317, 1949.
12. Madoff, I. M., Gaensler, E. A., and Strieder, J. W.: Congenital Absence of the Right Pulmonary Artery. Diagnosis by Angiocardiography, With Cardiorespiratory Studies, New England J. Med. **247**:149, 1952.

13. Fishman, A. P., Turino, G. M., Brandfonbrenner, M., and Himmelstein, A.: The "Effective" Pulmonary Collateral Blood Flow in Man, J. Clin. Invest. **37**:1071, 1958.
14. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease. II. Results of Preoperative Studies in Patients With Tetralogy of Fallot, Bull. Johns Hopkins Hosp. **80**:121, 1947.
15. Gray, F. D., Jr., Lurie, P., and Whittemore, R.: Circulatory Changes in Chronic Pulmonary Disease, Yale J. Biol. & Med. **23**:380, 1951.
16. Nakamura, T.: Pulmonary Circulation in Silicosis, Japanese Circ. J. **19**:12, 1956.
17. Theilen, E. V., Gregg, D. E., Paul, M. H., and Gilford, S. R.: Determination of Cardiac Output With the Cuvette Densitometer in the Presence of Reduced Arterial Oxygen Saturation, J. Appl. Physiol. **8**:330, 1955.
18. Fox, I. J., and Wood, E. H.: Applications of Dilution Curves Recorded From the Right Side of the Heart or Venous Circulation With the Aid of a New Indicator Dye, Proc. Staff Meet. Mayo Clin. **32**:541, 1957.
19. Fritts, H. W., Jr., Harris, P., Chidsey, C. A., III, Clauss, R. H., and Cournand, A.: Validation of a Method for Measuring the Output of the Right Ventricle in Man by Inscription of Dye Dilution Curves From the Pulmonary Artery, J. Appl. Physiol. **11**:362, 1957.
20. Cudkowicz, L., and Armstrong, J. B.: The Blood Supply of the Lung in Pulmonary Tuberculosis, Thorax **7**:270, 1952.
21. Wright, R. D.: The Blood Supply of Abnormal Tissues in the Lungs, J. Path. & Bact. **47**:489, 1938.
22. Cudkowicz, L., and Armstrong, J. B.: The Blood Supply of Malignant Pulmonary Neoplasms, Thorax **8**:152, 1953.
23. Calabresi, P., and Abelmann, W. H.: Porto-Caval and Porto-Pulmonary Anastomoses in Laennec's Cirrhosis and in Heart Failure, J. Clin. Invest. **36**:1257, 1957.
24. Roosenburg, J. G., and Deenstra, H.: Bronchial Pulmonary Vascular Shunts in Chronic Pulmonary Affections, Dis. Chest **26**:664, 1954.
25. Rivier, J. L., Reymond, C., and Desbaillets, P.: Trois cas d'anastomoses arterielles bronchopulmonaires demontrés par le catheterisme, Cardiologia **28**:357, 1956.
26. Cudkowicz, L., and Wraith, D. G.: A Method of Study of the Pulmonary Circulation in Finger Clubbing, Thorax **12**:313, 1957.
27. Visscher, M. B., and Johnson, J. A.: The Fick Principle: Analysis of Potential Errors in Its Conventional Application, J. Appl. Physiol. **5**:635, 1952-53.

The Simultaneous Estimation of Right and Left Ventricular Outputs Applied to a Study of the Bronchial Circulation in Patients With Chronic Lung Disease

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The enormous adaptability of the bronchial circulation to the alterations of pathologic circumstances has been well documented during the last two decades. The bronchial arteries normally lead into a capillary network which drains largely into the bronchial veins, thence into the azygos system, although some of the drainage of these capillaries may be into the pulmonary veins. In the normal dog this bronchial circulation accounts for only 0.5 to 1.5 per cent of the total left ventricular output.[1-3] Presumably, the human bronchial flow would be of a similar order.

Variations occur in the diseased state, so that direct anastomoses may be found between bronchial and pulmonary vessels, and the amount of bronchial blood drainage into the pulmonary veins may increase. New or expanded communications, both arterial and venous, have been clearly demonstrated anatomically.[4,5] Attempts have been made to measure the collateral bronchopulmonary flow[6-9]; accurate quantitation, however, has been elusive. The present report represents an attempt to estimate this flow by means of isotope dilution curves constructed from simultaneous sampling from the pulmonary and systemic arteries. In a steady state, and in the absence of other shunts, the difference between left and right ventricular outputs should represent mainly blood circulating through the bronchial arteries into the pulmonary veins via anastomoses. This would not affect the right ventricular output.

METHOD

A detailed description of the method has been presented in the preceding report.[10] Thirteen patients from the Veterans Administration Hospital, West Haven, Connecticut, were used in this study. The clinical details of this group are summarized in Table I.

One hour before cardiac catheterization, secobarbital sodium, 100 mg., was administered. A No. 9 cardiac catheter was introduced through a left antecubital vein to the main pulmonary

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TABLE I. CLINICAL DATA

PATIENT NUMBER	AGE (YR.)	CLINICAL DIAGNOSIS	CHEST X-RAY	FINGER-CLUBBING	HEMATOCRIT	MBC (L./MIN.)	VITAL CAPACITY (L.)	ARTERIAL O_2 SATURATION (%)
Group 1								
1.	52	Asthma	Normal	None	47	104	4.2	94
2.	37	Pheochromocytoma	Normal	None	46	124	3.7	93
3.	39	Recent hepatitis	Normal	None	42	—	—	98
4.	36	Asthenia	Old density. RUL	None	53	59	2.4	96
5.	26	Effort syndrome	Normal	None	50	—	—	93
Group 2								
6.	51	Bronchiectasis, fibrosis, cor pulmonale	Confirmed clinical diagnosis	Drumstick	43	62	3.5	87
7.	39	Bilateral bronchiectasis	Confirmed clinical diagnosis	Drumstick	47	61	1.5	88
8.	60	Bronchiectasis, healed apical tuberculosis	Confirmed clinical diagnosis	Drumstick	52	—	1.2	88
9.	69	Emphysema and bronchiectasis	RML + RLL ectasia	Almost drumstick	42	24	2.0	91
Group 3								
10.	42	Bilateral tuberculosis	Bilateral cavities	None	50	52	1.4	87
11.	47	Old left tuberculosis	Left pulmonary fibrosis	None	49	103	4.1	88
12.	65	Old bilateral apical tuberculosis and fibrosis	Bilateral fibrosis	None	62	17	1.3	86
13.	61	Pulmonary fibrosis	Old bilateral apical tuberculosis with fibrosis	None	39	—	—	90

artery. Within 5 minutes following estimation of the cardiac output by the Fick method, radioactive iodinated serum albumin (RISA), having an activity of about 5 μc, was displaced from a weighed tuberculin syringe through the right-angled limb of a three-way stopcock into a polyethylene catheter, which had a dead space well in excess of the isotope volume.* At a signal the isotope was washed as a bolus into the superior vena cava, with about 15 times its volume of saline. Beginning with the injection of the isotope, samples of about 1.1 ml. of blood were aspirated at one-second intervals from both the femoral and pulmonary arteries by means of two double-valved Cornwall syringes, and the aliquots discharged at the same rate into the 29 tubes of each of two synchronously revolving fractional collectors. At the end of the injection the syringe was reweighed and the polyethylene catheter and its attachments were removed and washed out with 250 ml. of saline. The total amount of RISA injected was calculated from the formula:

$$\text{"I"} = \frac{\text{Counts in standard} \times \text{Weight of dose injected}}{\text{Weight of standard}} - \text{Counts in washout,}$$

where "I" is the amount injected in counts. The average number of counts per 1 ml. of aliquot per minute was determined for each tube in a scintillation well-counter and plotted on semilogarithmic paper. The sum of the ordinates at one-second intervals was calculated from each curve on a base line representing 0.1 per cent of the peak value. The outputs from each ventricle were then obtained from the Stewart-Hamilton formula:

$$F = \frac{\text{"I"} \times 60}{\text{Area under the curve}}.$$

The difference between left ventricular ($\dot{Q}_{LV}$) and right ventricular output ($\dot{Q}_{RV}$) represents the indirect estimate of bronchopulmonary collateral flow ($\dot{Q}_{BA}$).[10]

RESULTS

The data obtained are divided into three groups according to the original clinical designation of the patients. The results for Group 1, the patients used as controls, are given in Table II. In Patient 3 a difference was recorded between the right and left ventricular outputs, with the right exceeding that of the left by 4.1 per cent, which is higher than the average difference in the other four patients, in whom the mean difference of the left ventricular output over that of the right is 1.5 per cent. The very high cardiac output in this patient and the higher right ventricular output remains unexplained.

Table III summarizes the estimates of bronchial arterial flow in Group 2, four patients with bronchiectasis and finger-clubbing. These patients were studied because earlier reports have indicated that bronchiectasis and clubbing are associated with precapillary bronchopulmonary anastomoses.[11] The average difference between the left and right minute flows in these four patients was 17.9 per cent.

Figs. 1 and 2 show the semilogarithmic and rectilinear plots of Patient 7. The appearance time is 1 second for the right ventricle and 7.8 seconds for the left. The peak of the left ventricular curve is considerably lower than that of the right. The symmetry on the rectilinear plot has been lost and there is considerable widening of the base of the left ventricular curve as well as a step in the lower quarter of the downslope.

*The total dose of RISA was so small that, even in the event that the procedure were repeated, the total dosage was well within safe limits for the patient.

The four patients in Group 3 had pulmonary tuberculosis, which was active in Patient 12 and quiescent in the others. Patients with tuberculosis have been found to have large bronchial arterial flows, by virtue of dilatation and proliferation of the bronchial arteries in the areas of the pulmonary lesions. The venous drainage from these channels is unknown but probably leads into the pulmonary veins without communicating with the pulmonary arteries.[12] The data for these four patients are summarized in Table IV. The average difference between the left and right ventricular outputs is 8.1 per cent.

TABLE II. RESULTS OBTAINED FROM 5 PATIENTS IN WHOM THERE WAS NO REASON TO SUSPECT ABNORMAL PULMONARY CIRCULATION

PATIENT NUMBER	$\dot{Q}_{RV}$ (L./MIN.)	$\dot{Q}_{LV}$ (L./MIN.)	$\dot{Q}_{BA}$ (L./MIN.)	$\dot{Q}_{BA}$ AS PER CENT OF $\dot{Q}_{LV}$	SYSTEMIC FLOW (FICK) (L./MIN.)
1.	5.99	5.99	0.00	0.0	4.76
2.	4.89	5.03	0.14	2.8	4.94
3.	16.64	15.98	−0.66	−4.1	15.00
4.	6.58	6.69	0.11	1.6	5.65
5.	6.13	6.23	0.10	1.6	6.88

$\dot{Q}_{RV}$ = Right ventricular output.
$\dot{Q}_{LV}$ = Left ventricular output.
$\dot{Q}_{BA}$ = Bronchial flow.

TABLE III. RESULTS OBTAINED FROM 4 PATIENTS SUSPECTED OF HAVING INCREASED BRONCHIAL FLOW

PATIENT NUMBER	$\dot{Q}_{RV}$ (L./MIN.)	$\dot{Q}_{LV}$ (L./MIN.)	$\dot{Q}_{BA}$ (L./MIN.)	$\dot{Q}_{BA}$ AS PER CENT OF $\dot{Q}_{LV}$	SYSTEMIC FLOW (FICK) (L./MIN.)
6.	3.87	4.72	0.85	18.0	7.64
7.	7.93	9.78	1.85	18.9	9.95
8.	5.89	7.38	1.49	20.2	4.29
9.	5.53	6.47	0.94	14.5	5.25

TABLE IV. RESULTS OBTAINED FROM 4 PATIENTS WITH PULMONARY TUBERCULOSIS

PATIENT NUMBER	$\dot{Q}_{RV}$ (L./MIN.)	$\dot{Q}_{LV}$ (L./MIN.)	$\dot{Q}_{BA}$ (L./MIN.)	$\dot{Q}_{BA}$ AS PER CENT OF $\dot{Q}_{LV}$	SYSTEMIC FLOW (FICK) (L./MIN.)
10.	9.75	10.85	1.1	10.1	7.78
11.	4.66	4.97	0.31	6.2	4.87
12.	7.09	7.95	0.86	10.8	5.74
13.	8.58	9.06	0.48	5.3	4.36

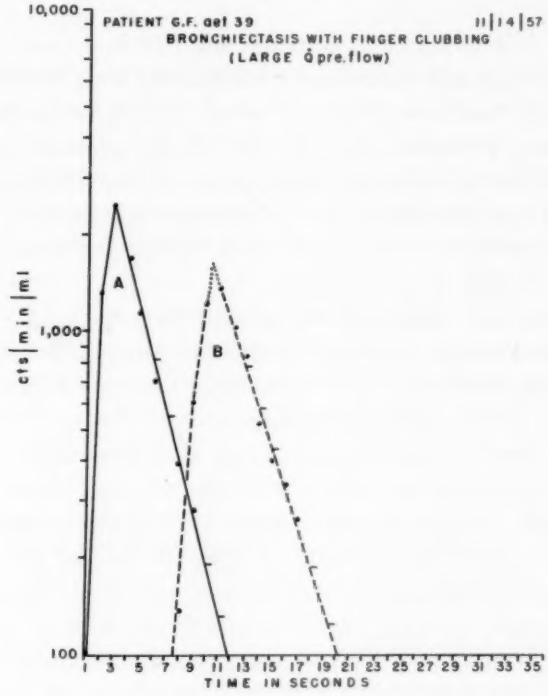

Fig. 1.

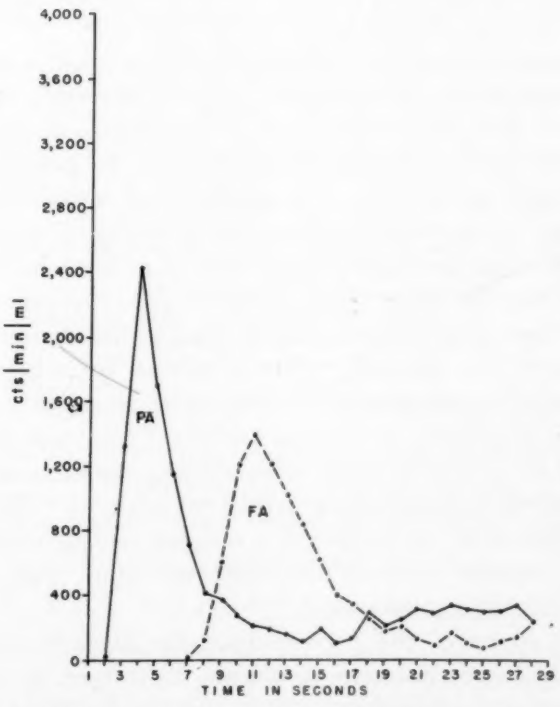

Fig. 2.

Fig. 1.—Semilogarithmic plot of the results obtained from a patient with finger-clubbing. *A:* Pulmonary arterial curve. *B:* Femoral arterial curve. *cts/min/ml* = counts per minute per milliliter.

Fig. 2.—Rectilinear plot of the data represented in Fig. 1. *PA:* Pulmonary arterial curve. *FA:* Femoral arterial curve. *cts/min/ml* = counts per minute per milliliter.

DISCUSSION

The finding of left ventricular outputs slightly in excess of right ventricular outputs in 3 out of 5 patients who had no apparent lung disease might be due to the bronchial arterial flow returning to the left ventricle via the pulmonary veins in the normal man. However, the pitfalls of the present method which have been described elsewhere preclude the assumption that differences in the magnitude reported here are reliable. The differences between the indicator dilution and the Fick measurements are within the limits reported by other workers, except perhaps in Patient 1.

In the patients with finger-clubbing and chronic lung disease the present method shows a less ambiguous trend, yielding a mean difference of 17.9 per cent. Patients of this type are known to have enlarged bronchial arteries and extensive bronchopulmonary precapillary anastomoses.[4]

Evidence has been presented indicating that bronchial arterial blood flow through these communications mixes with the venous blood of the pulmonary arteries.[8,13] Finding a larger left than right ventricular output could, therefore, be anticipated. As in the dog experiments reported in the accompanying paper,[10] blood flowing through these bronchopulmonary arterial anastomoses returns to the left heart through alveolar capillaries and pulmonary veins. It has been suggested in other studies[8,11,14] that the increase in left ventricular load induced by this additional, one-sided circulation could explain the left ventricular hypertrophy frequently found in the absence of other causes in patients with chronic lung disease.[15-17]

In patients with pulmonary tuberculosis the anatomic evidence points to a considerable enlargement of bronchial arterial branches in the tuberculous area.[12] Although an increase in bronchial arterial flow could be anticipated, the route of the venous return is by no means certain. In previous studies no evidence has been found at autopsy that precapillary anastomoses developed in this type of patient. It is of interest that the tuberculous patients in this series had low arterial blood oxygen saturations, and mean bronchial flow estimated to be 8.1 per cent of the left ventricular output. This suggests that at least part of the bronchial flow found its way into the pulmonary vessels, presumably through expansion of the normally present venous bronchopulmonary anastomoses. Complicating emphysematous changes are frequently seen in old tuberculous lesions. An expansion of venous collateral channels, known to occur in emphysema,[5] may be a further factor in producing the large differences between right and left ventricular outputs observed in out patients. Data on independent measurement of right and left ventricular outputs in this third modality of expanded bronchial vessels are not available, although some indirect evidence suggests their functional significance.[18,19]

The potential errors of the Fick method for measurement of the cardiac output, particularly in the presence of shunts, have been discussed elsewhere.[10] Although the values of cardiac output obtained by the direct application of the Fick principle have been charted for each patient in this series, no attempt has been made to estimate the variance between this method and the indicator dilution technique, or to interpret the mechanisms involved.

SUMMARY

A method of estimating the difference between the outputs of the two ventricles, using radioactive iodinated serum albumin in a dilution technique of simultaneous right and left ventricular output determinations, has been applied to 13 patients. The difference in the outputs between the left and right ventricles constitutes an indirect estimate of bronchial arterial flow returning to the left side of the heart through the pulmonary veins. In 3 out of 5 patients who had no lung disease a mean difference of 1.5 per cent between the two outputs was found. One of the 5 had no difference, and one had a larger right ventricular output. In 4 patients with finger-clubbing and bronchiectasis the mean difference observed was 17.9 per cent. In the last group of 4 patients with pulmonary tuberculosis, a mean difference of 8.1 per cent was found.

REFERENCES

1. Bruner, H. D., and Schmidt, C. F.: Blood Flow in the Bronchial Artery of the Anesthetized Dog, Am. J. Physiol. **148**:648, 1947.
2. Daly, M. DeB., Aviado, D. M., and Lee, C. Y.: The Contribution of the Bronchial Circulation to the Venous Admixture in Pulmonary Venous Blood, 19th International Physiological Congress, Montreal, 1953, p. 298.
3. Salisbury, P. F., Weil, P., and State, D.: Factors Influencing Collateral Blood Flow to the Dog's Lung, Circulation Res. **5**:303, 1957.
4. Liebow, A. A., Hales, M. R., and Lindskog, G. E.: Enlargement of the Bronchial Arteries and Their Anastomoses With the Pulmonary Arteries in Bronchiectasis, Am. J. Path. **25**:211, 1949.
5. Liebow, A. A.: The Bronchopulmonary Venous Collateral Circulation, With Special Reference to Emphysema, Am. J. Path. **29**:251, 1953.
6. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease. II. Results of Preoperative Studies in Patients With Tetralogy of Fallot, Bull. Johns Hopkins Hosp. **80**:121, 1947.
7. Bloomer, W. E., Harrison, W., Lindskog, G. E., and Liebow, A. A.: Respiratory Function and Blood Flow in the Bronchial Artery After Ligation of the Pulmonary Artery, Am. J. Physiol. **157**:317, 1949.
8. Gray, F. D., Jr., Lurie, P., and Whittemore, R.: Circulatory Changes in Chronic Pulmonary Disease, Yale J. Biol. & Med. **23**:380, 1951.
9. Nakamura, T.: Pulmonary Circulation in Silicosis, Japanese Circ. J. **19**:12, 1956.
10. Cudkowicz, L., Calabresi, M., Nims, R. G., and Gray, F. D., Jr.: The Simultaneous Estimation of Right and Left Ventricular Outputs Applied to a Study of Bronchial Circulation in Dogs, Am. Heart J. **58**:732, 1959.
11. Liebow, A. A., Hales, M. R., Harrison, W., Bloomer, W., and Lindskog, G. E.: The Genesis and Functional Implications of Collateral Circulation of the Lungs, Yale J. Biol. & Med. **22**:637, 1950.
12. Cudkowicz, L., and Armstrong, J. B.: The Blood Supply of the Lung in Pulmonary Tuberculosis, Thorax **7**:270, 1952.
13. Cudkowicz, L., and Wraith, D. G.: A Method of Study of the Pulmonary Circulation in Finger Clubbing, Thorax **12**:313, 1957.
14. Alley, R. D., Stranahan, A., Kausel, H., Formel, P., and Van Mierop, L. H. S.: Demonstration of Bronchial-Pulmonary Artery Reverse Flow in Suppurative Pulmonary Disease, Clin. Res. **6**:41, 1958.
15. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, Am. Heart J. **11**:163, 1936.
16. Scott, R. W., and Garvin, C. F.: Cor Pulmonale: Observations in Fifty Autopsy Cases, Am. Heart J. **22**:56, 1941.
17. Spain, D. M., and Handler, B. J.: Chronic Cor Pulmonale, Arch. Int. Med. **77**:37, 1946.
18. Gray, F. D., Jr., Williams, M. H., and Gray, F. G.: The Circulatory and Ventilatory Changes in Chronic Pulmonary Disease as Affected by Lanatoside C, Am. Heart J. **44**:517, 1952.
19. Calabresi, M., and Ciampa, T.: Unpublished data.

Effect of Various Drugs on Spontaneous and Surgically Induced Ventricular Fibrillation in Hypothermia

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Numerous experimental studies have been carried out in an attempt to discover a drug which will prevent the occurrence of ventricular fibrillation at low body temperatures.[1,2] As yet no general agreement exists concerning the effectiveness of any particular antifibrillary drug in hypothermia. This lack of agreement stems at least partially from two factors which are not actually related to the particular drugs tested to date. Ventricular fibrillation may occur spontaneously during hypothermia[3] or may be induced by physical manipulation of the heart as in the performance of intracardiac surgery.[4] These two conditions are not entirely similar although hypothermia is common to both. A second fact to be considered is that those animals which fail to fibrillate spontaneously during hypothermia cool to a point at which asystole occurs. Asystole is a rather arbitrary end point. Often hypothermic animals will show no cardiac activity for several minutes, then resume beating, and later develop ventricular fibrillation. Thus, the frequency of asystole in hypothermia may be determined in part by the definition of asystole.

The present investigation is concerned with evaluating the effectiveness of three pharmacologic agents, Ambonestyl†, quinidine, and mephentermine,‡ as antifibrillary drugs in hypothermia with and without the added complication of cardiac surgery. All three drugs have been shown to be effective against a variety of experimentally produced arrhythmias in normothermic dogs.[5-7] In addition, Ambonestyl[8] and quinidine[9] were reported to reduce the frequency of surgically induced fibrillation in hypothermia, but little information is available concerning their use against spontaneous fibrillation. Mephentermine, on the other hand, reduced significantly the incidence of spontaneous fibrillation, with no data presented regarding its action on the induced type of fibrillation.[10]

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†2 diethyl-aminoethyl-isonicotinamide hydrochloride (MC 4112), furnished by the Squibb Institute for Medical Research.

‡Mephentermine sulfate (Wy mine), furnished by Wyeth Laboratories, Inc.

METHODS

Apparently healthy mongrel dogs of both sexes, ranging in weight from 7.0 to 16.0 kilograms, were anesthetized with pentobarbital sodium (30 mg./Kg. intravenously), supplemented as needed to suppress shivering. The external jugular vein and common carotid artery on opposite sides were exposed for the injection of drugs and the manometric recording of blood pressure, respectively. Placement of standard limb leads for electrocardiographic recordings and insertion of an endotracheal tube and a rectal thermometer completed the precooling preparations. Hypothermia was induced by covering all but the head and neck with crushed ice. Positive pressure artificial respiration was instituted in all animals at a rectal temperature of 30°C.

In the initial series of experiments concerned with spontaneous fibrillation, the dogs were allowed to cool without interruption until death, i.e., until ventricular fibrillation (VF) or asystole appeared on the electrocardiogram. Asystole in the present study is defined as the absence of electrocardiographic activity for a minimum period of 10 minutes. Confirmation of VF or asystole was made by opening the thoracic cage and observing the heart directly.

In the second portion of this investigation, surgically induced VF was studied. Dogs were cooled to a rectal temperature of 27°C., at which point the covering of ice was removed. A right thoracotomy at the fifth intercostal space was performed and the pericardium incised longitudinally. Venous inflow was occluded (for 10 minutes) by clamping the superior and inferior venae cavae and the azygos vein. A 2-cm. incision was made in the right ventricular wall and the interior of the right chamber digitally palpated (during the period of circulatory stasis). The incision was then closed with four or five sutures. After a total of 10 minutes of venous occlusion, circulation was re-established. At the time of cardiac surgery, rectal temperature was usually stabilized at 25°C. Following the re-establishment of normal circulation, all dogs were observed for a period of 10 minutes. The development of a fibrillary state at any time during or following the surgical procedure just described was defined as induced VF.

In the series of experiments without cardiac manipulation, Ambonestyl hydrochloride (20 to 80 mg./Kg.), quinidine sulfate (8 to 16 mg./Kg.), and mephentermine sulfate (1.5 to 6.0 mg./Kg.) were administered intravenously at a rectal temperature of 25°C. Because of the short duration of action of Ambonestyl[6] a second dose was given 1 hour after the initial injection. In those animals subjected to hypothermia and cardiac surgery these three agents were injected intravenously in the same dose range as above but at a rectal temperature of 30°C.

Finally, combinations of (a) Ambonestyl (40 mg./Kg.) and quinidine (16 mg./Kg.), (b) Ambonestyl (40 mg./Kg.) and mephentermine (3 mg./Kg.), and (c) quinidine (16 mg./Kg.) and mephentermine (3 mg./Kg.) were tested against spontaneous VF alone. All were administered intravenously at a rectal temperature of 25°C.

RESULTS

Spontaneous Ventricular Fibrillation.—Table I summarizes the data obtained on 146 dogs subjected to hypothermia without cardiac manipulation. In 41 control dogs the average rectal temperature at the time of death was 17.2°C. Of these 41 dogs, 30 (73 per cent) died in ventricular fibrillation. Mephentermine sulfate in a dose of 3 mg./Kg. was capable of significantly reducing the incidence of spontaneous VF ($P = < 0.05$). The effective dose range of mephentermine apparently is quite limited, since neither 1.5 nor 6 mg./Kg. exhibited significant antifibrillary activity. Ambonestyl and quinidine in the doses used demonstrated no protective action against spontaneous VF.

The statement made above, viz., that the frequency of asystole may be determined in part by the definition of asystole, is supported by a consideration of the quinidine-treated dogs. On several occasions dogs in this group showed periods of cardiac arrest of 1 to 4 minutes' duration, then resumed beating, and eventually suffered a fibrillary death. If asystole had been defined as electro-

cardiographic inactivity for a period of 1 minute, then the frequency of VF would have been significantly reduced to 17 per cent in the 23 quinidine-treated animals.

The effects of various combinations of the three drugs on the incidence of spontaneous VF are also shown in Table I. Combination of Ambonestyl (40 mg./Kg.) and quinidine (16 mg./Kg.) exerted no beneficial effect, whereas both combinations in which mephentermine (3 mg./Kg.) was included significantly reduced the incidence of VF. Neither combination exerted a greater effect than did mephentermine alone.

TABLE I. THE EFFECTS OF AMBONESTYL, QUINIDINE, AND MEPHENTERMINE ON SPONTANEOUS VENTRICULAR FIBRILLATION IN THE HYPOTHERMIC DOG

DRUG	DOSE (MG./KG.)	NUMBER OF DOGS	NUMBER OF DOGS FIBRILLATING	TERMINAL TEMPERATURES (°C. AVERAGE ± S.D.)	
				RECTUM	HEART
Control	—	41	30 (73%)	17.7 ± 3.9	17.6 ± 3.2
Ambonestyl	20	5	4 (80%)	16.9 ± 3.6	15.8 ± 3.3
	40	10	5 (50%)	15.9 ± 3.0	16.5 ± 2.3
	80	8	4 (50%)	14.9 ± 2.5	15.5 ± 2.0
Quinidine	8	10	7 (70%)	17.0 ± 2.8	16.8 ± 2.4
	12	5	4 (80%)	16.0 ± 3.0	15.1 ± 2.9
	16	8	4 (50%)	16.4 ± 2.7	15.9 ± 2.8
Mephentermine	1.5	5	4 (80%)	15.1 ± 4.7	16.2 ± 3.4
	3	10	3 (30%)*	15.7 ± 1.9	15.6 ± 2.5
	6	6	4 (67%)	17.3 ± 5.0	16.8 ± 4.2
Ambonestyl and Quinidine	40 16	8	4 (50%)	12.8 ± 3.7**	14.0 ± 2.7**
Ambonestyl and Mephentermine	40 3	10	3 (30%)*	14.5 ± 4.2**	16.3 ± 2.7
Quinidine and Mephentermine	16 3	20	4 (20%)*	14.3 ± 2.8**	14.2 ± 2.2**

*Statistically significant at 0.05 level (chi square test).
**Statistically significant at 0.05 level (t test).

TABLE II. THE EFFECTS OF AMBONESTYL, QUINIDINE, AND MEPHENTERMINE ON SURGICALLY INDUCED VENTRICULAR FIBRILLATION IN THE HYPOTHERMIC DOG

DRUG	DOSE (MG./KG.)	NUMBER OF DOGS	NUMBER OF DOGS FIBRILLATING	P VALUE
Control	—	20	12 (60%)	—
Ambonestyl	20	7	4 (57%)	>0.7
	40	10	2 (20%)	<0.1> 0.05
	80	5	3 (60%)	>0.5
Quinidine	8	10	5 (50%)	>0.9
	12	10	0. (0%)	<0.01
Mephentermine	1.5	6	3 (50%)	>0.9
	3	5	4 (80%)	>0.7
	6	5	4 (80%)	>0.7

Induced Ventricular Fibrillation.—The effect of Ambonestyl, quinidine, and mephentermine on the frequency of VF induced by cardiac manipulation at a rectal temperature of 25°C. is detailed in Table II. Quinidine in a dose of 12 mg./Kg. provided complete protection in a series of 10 dogs. The lower dose of 8 mg./Kg. did not significantly decrease the number of fibrillators. The administration of 40 mg./Kg. of Ambonestyl reduced the incidence of induced VF to 20 per cent, a frequency which, however, was not significantly different from the control frequency of 60 per cent ($P = > 0.05, < 0.1$). The other two doses of Ambonestyl proved to be completely ineffective, as did all three doses of mephentermine.

DISCUSSION

The term hypothermic ventricular fibrillation has been used in the literature to describe both VF which occurs spontaneously in dogs rendered hypothermic and that which is produced by some form of cardiac manipulation.[3,4] The present study indicates that these two conditions are not entirely similar and should be carefully differentiated, especially when testing the efficacy of various drugs as antifibrillary agents in hypothermia. For example, the data presented here and elsewhere indicate that quinidine,[9] especially, and Ambonestyl,[10] to a lesser degree, do provide protection against the induced type of VF. Yet neither agent altered the incidence of spontaneous VF. On the other hand, mephentermine appears capable of reducing the frequency of spontaneous but not induced VF. Another distinction between spontaneous and induced fibrillation is the temperature range at which the fibrillation occurs. Induced fibrillation is easily produced at rectal temperatures of 25 to 30°C., whereas spontaneous VF rarely occurs above 25°C.

The differential effect of quinidine and mephentermine on the two types of VF in hypothermia is of interest in view of the fact that these two drugs have been shown to alter the basic properties of normothermic cardiac muscle in opposite directions. Thus, quinidine decreases excitability, decreases conduction velocity, and prolongs the refractory period, whereas mephentermine increases excitability, increases conduction velocity, and shortens the refractory period.[6,11] If one can assume that similar effects are exerted on the hypothermic heart, then one may gain some insight into the factors which initiate or prevent the two types of VF under consideration. It is tempting to hypothesize from the data obtained that (1) cardiac manipulation incites the firing of multiple ectopic foci which leads ultimately to disorganized fibrillary activity, and (2) depression of ventricular excitability and/or lengthening of the refractory period should decrease this tendency toward ectopic beats and fibrillation. The results obtained with quinidine and mephentermine support this hypothesis. The Ambonestyl data are also in general agreement with this hypothesis, since this agent has been reported to prolong the refractory period of the normal heart, with little or no effect on excitability or conduction velocity.[5] In addition, Dactil* was shown to

*Piperidolate hydrochloride, Lakeside Laboratories.

decrease surgically induced VF in the hypothermic dog, presumably by prolonging the refractory period and depressing excitability.[12] One may hypothesize further that in contrast to surgically induced VF, spontaneous VF may be more accurately related to the marked decrease in ventricular conduction velocity which occurs at low temperatures. Such a relationship was suggested initially by the data of Garcia-Ramos.[13] Thus, drugs which increase conduction velocity should be effective in preventing spontaneous VF in hypothermia. Again, the results obtained in this study would support this contention. In this regard, norepinephrine also has been stated to increase the tolerance of dogs to profound hypothermia,[14] whereas procaine amide, which decreases conduction velocity, was of no value against spontaneous hypothermic fibrillation.[2]

SUMMARY

The antifibrillary actions of Ambonestyl, quinidine, and mephentermine were studied on spontaneous ventricular fibrillation and on surgically induced ventricular fibrillation in the hypothermic dog. In addition, combinations of these agents were studied on spontaneous ventricular fibrillation in hypothermia. Mephentermine in a dose of 3 mg./Kg. significantly reduced the frequency of spontaneous ventricular fibrillation, whereas Ambonestyl and quinidine were not effective. When combined with either Ambonestyl or quinidine, mephentermine exerted the same antifibrillary effect. Surgically induced ventricular fibrillation in hypothermia was significantly reduced by quinidine (12 mg./Kg.) but not by Ambonestyl or mephentermine. The results indicate that the two situations (spontaneous and surgically induced fibrillation in hypothermia) are not entirely similar, that prevention of one does not imply prevention of the other, and that the factors predisposing the heart to fibrillation are different in the two conditions.

REFERENCES

1. Riley, P. A., Mixon, B. M., and Barila, T. G.: Surgery **42**:936, 1957.
2. Covino, B. G., Wright, R., and Charleson, D. A.: Am. J. Physiol. **181**:54, 1955.
3. Covino, B. G., Charleson, D. A., and D'Amato, H. E.: Am. J. Physiol. **178**:148, 1954.
4. Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V.: Ann. Surg. **138**:360, 1953.
5. Lanzoni, V., and Clark, B. B.: Circulation Res. **3**:335, 1955.
6. Dawes, G. S.: Pharmacol. Rev. **4**:43, 1952.
7. Lynch, P. R., Webber, D. L., and Oppenheimer, M. J.: Anesthesiology **16**:632, 1955.
8. Covino, B. G., and Hegnauer, A. H.: Surgery **40**:475, 1956.
9. Berman, E. J., Taylor, M. T., and Fisch, C.: J. Thoracic Surg. **35**:483, 1958.
10. Covino, B. G.: J. Pharmacol. & Exper. Therap. **122**:418, 1958.
11. Stewart, G. H., Lynch, P. R., Barrera, F., and Oppenheimer, M. J.: Am. J. Physiol. **186**:513, 1956.
12. Hara, M., Harberg, F. J., and Hudson, L. H.: A.M.A. Arch. Surg. **75**:780, 1957.
13. Garcia-Ramos, J.: J. Thoracic Surg. **31**:635, 1956.
14. Kuhn, L. A., and Turner, J. K.: Circulation Res. **7**:366, 1959.

Case Reports

Spontaneous Subarachnoid Hemorrhage Simulating Acute Myocardial Infarction

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The report to follow concerns a case in which the presence of chest pain, the absence of the usual clinical signs and symptoms of subarachnoid bleeding, and the presence of S-T and T-wave changes in the electrocardiogram suggesting myocardial "ischemia" and "injury" led to the erroneous diagnosis of acute myocardial infarction in a patient with spontaneous subarachnoid hemorrhage and no heart disease. It has been demonstrated previously that lesions in the central nervous system and certain manipulations of the brain and its vasculature may be associated with transient electrocardiographic changes. Burch[1] first called attention to electrocardiographic changes in cerebrovascular accidents, and in a review of the nonspecificity of the electrocardiogram in coronary artery disease, Levine[2] published the tracing of an elderly comatose woman whose electrocardiogram showed widespread "ischemic" T-wave changes, and who at autopsy was found to have a ruptured aneurysm of the circle of Willis and no demonstrable heart disease. An erroneous antemortem diagnosis of myocardial infarction had been made in Levine's case. Burch and associates[3] were able to collect several cases of cerebrovascular accidents associated with some electrocardiographic changes and frequently noted T waves of large amplitude and duration which were often negative in the standard and chest leads. Poole[4] reported arrhythmias, S-T segment changes, and T-wave changes during manipulation of the circle of Willis under certain conditions of hypothermia and light anesthesia in the human being.

CASE REPORT

A 37-year-old white woman "fainted" in her bathroom, remained unconscious one-half hour, and was incontinent of urine and feces. When admitted to the hospital an hour later she was pale, sweaty, and stuporous. The blood pressure was 120 mm. Hg systolic and 80 diastolic, and

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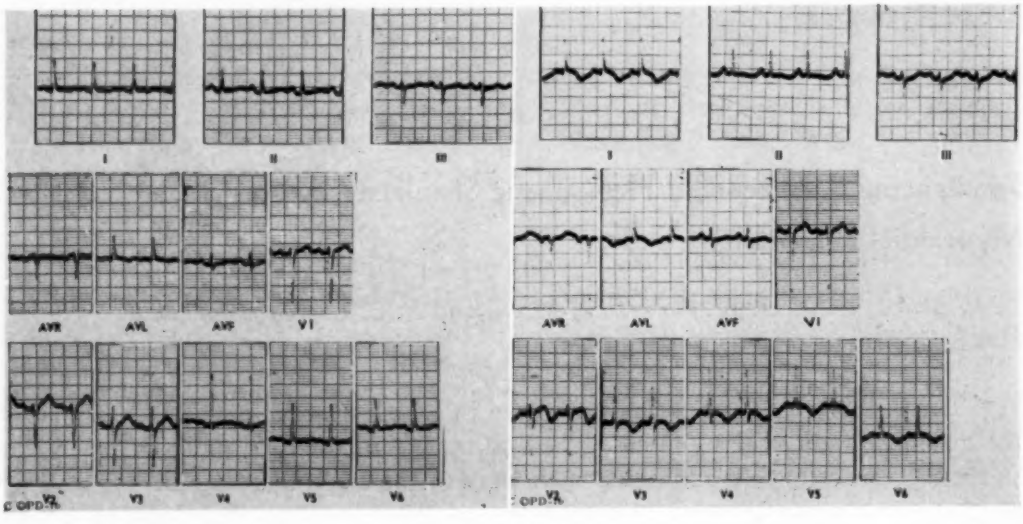
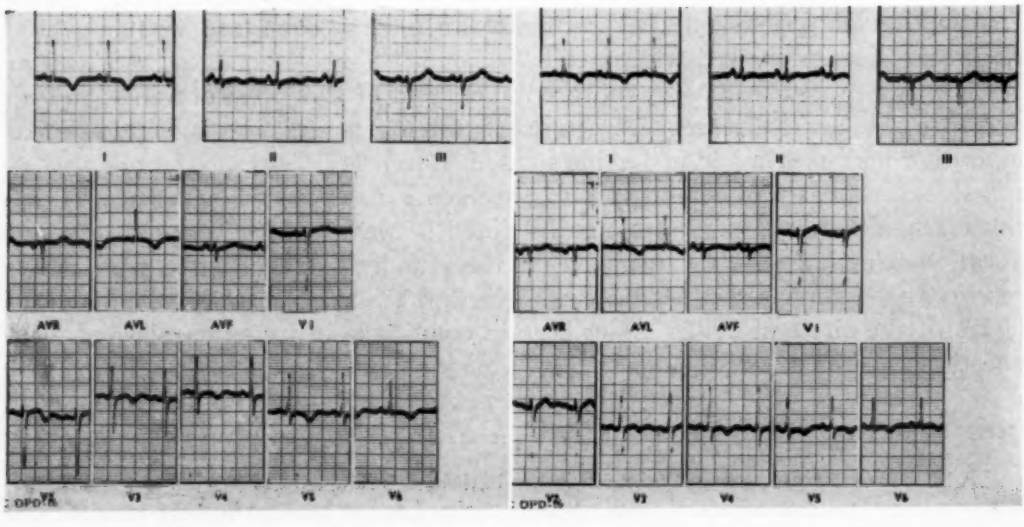
the pulse was 110. A gallop rhythm was heard at the cardiac apex, but the remainder of a physical examination was negative. There were no reflex changes and no nuchal rigidity or headache. Three hours after admission to the hospital she complained of severe substernal pain which radiated to the back. Blood pressure was 140 mm. Hg systolic and 90 diastolic, and the pulse was 120 at this time. The severe pain lasted 30 minutes, but there was no headache. She had experienced one previous episode of unconsciousness 6 months before, lasting only a few minutes. She



A. *B.*

Fig. 1.—The electrocardiogram taken on the day of admission (*A*) shows minimal nonspecific T-wave changes, which became more marked by the following day (*B*) and suggested anterior myocardial ischemia.



A. *B.*

Fig. 2.—Electrocardiograms taken 6 days (*A*) and 9 days (*B*) after admission.

was known to have gallstones. Her father had died of a myocardial infarction at the age of 50 years. Complete blood count and urinalysis were normal except for a leukocytosis of 13,700 on admission. An electrocardiogram taken on the day of admission (Fig. 1,*A*) showed nonspecific T-wave changes, but by the following day (Fig. 1,*B*) there were deeply inverted T waves in Leads I, aV_L, and V_2 through V_6. The S-T segments in Lead V_2 showed elevation and "coving" suggestive of subepicardial injury. Electrocardiograms taken at intervals over the next 2 weeks showed

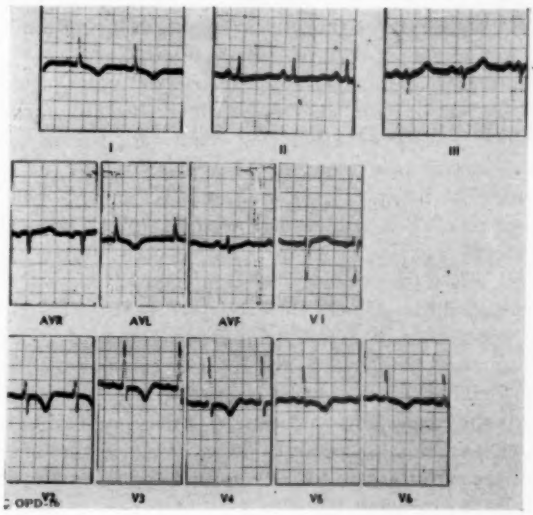


Fig. 3.—Electrocardiogram taken at the time of the second episode of subarachnoid bleeding and generalized convulsion.

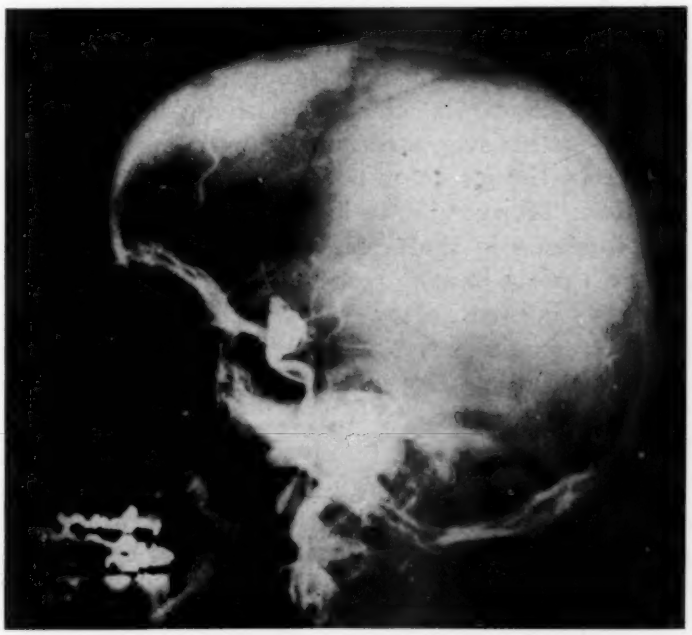


Fig. 4.—Cerebral angiogram showing aneurysm at junction of right internal carotid and middle cerebral arteries.

variations of these changes, which at times were thought to be the evolutionary changes of an acute myocardial infarction, but never showed diagnostic changes in the QRS complexes (Fig. 2). An electroencephalogram taken on the day after admission was within normal range. After 3 days in the hospital the patient experienced generalized headache, but no nuchal rigidity. By this time the apical gallop was no longer present. The headache gradually abated over a 4-day period. Because of the normal electroencephalogram and the absence of signs of meningeal irritation, lumbar puncture was not done. Chest and skull x-rays were normal, and the leukocytosis gradually disappeared. Because it was felt that anterior myocardial infarction was the most likely diagnosis, anticoagulant treatment was begun. During the next 3 weeks the patient was asymptomatic, and at the end of that time she was dismissed.

After 1 week at home she experienced a generalized convulsion, severe headache, and was readmitted to the hospital, conscious and lucid, but with marked and unmistakable nuchal rigidity. A lumbar puncture yielded grossly bloody spinal fluid. An electrocardiogram (Fig. 3) again showed deeply inverted T waves over most of the precordium. Prothrombin activity was immediately returned to normal with intravenous vitamin K_1 oxide. The headache gradually improved after 2 days of bed rest. Bilateral carotid arteriography 5 days after admission showed a large, multilobulated aneurysm arising from the internal carotid artery on the right. It seemed to extend both above and below the clinoid processes (Fig. 4).

Intracranial ligature and obliteration of the aneurysm was attempted, but the entire aneurysm could not be visualized because of its extension into the sphenoid bone. When packing of the area with muscle failed to stop the bleeding, the right internal carotid artery was ligated in the neck. The patient never regained consciousness after the procedure and died on the third postoperative day. At autopsy the aneurysm was seen to extend approximately 2 cm. into the substance of the sphenoid bone, and it was necessary to remove a portion of bone in order to visualize it completely. The coronary arteries were entirely normal and there was no evidence of myocardial infarction on gross or microscopic examination.

DISCUSSION

The clinical importance of subarachnoid bleeding as a cause of electrocardiographic changes suggesting myocardial infarction should be obvious. Diagnosing this lesion may not be without difficulty, as in Levine's case in which the patient was comatose or as in the case reported here in which chest pain, relative hypotension, tachycardia associated with a gallop rhythm, leukocytosis, and low-grade fever further suggested myocardial infarction. The present case was further confused by the absence of the nuchal rigidity typical of subarachnoid bleeding and the delay of several days in onset of any headache. Serum levels of oxalacetic transaminase in the present case were normal during the first 3 days, a finding which might have provoked suspicion that the diagnosis of myocardial infarction was in error. However, it is conceivable that subarachnoid hemorrhage might even raise serum levels of this enzyme if brain tissue were destroyed, since such elevations have been demonstrated in experimental cerebral infarction.[5]

The authors advance no explanation for the mechanism of the electrocardiographic changes noted. Certainly, such changes would not be likely on a basis of myocardial ischemia from coronary artery disease, which was absent. It also seems unlikely that myocardial ischemia could have been present from shock or diminished cardiac output, since arterial blood pressure did not remain extremely low for any protracted length of time.

Burch[3] suggested the possibility of some electrolyte disturbance as a causative factor, and Poole[4] has postulated that hemorrhage within and around the

walls of an intracranial aneurysm may render its intrinsic nerves and musculature hyperirritable and, thus, originate unusual vasomotor reflexes. No evidence is available from the present case which would lend support to, or discredit, either of these possibilities.

SUMMARY

That spontaneous subarachnoid hemorrhage causing electrocardiographic changes may be confused with acute myocardial infarction is illustrated by a case with some clinical features suggestive of myocardial infarction and without certain of the usual signs and symptoms of subarachnoid bleeding.

REFERENCES

1. Burch, G. E.: Personal communication cited by Levine.[2]
2. Levine, H. D.: Nonspecificity of the Electrocardiogram Associated With Coronary Artery Disease, Am. J. Med. **15**:344, 1953.
3. Burch, G. E., Meyers, R., and Abildskov, J. A.: New Electrocardiographic Pattern Observed in Cerebrovascular Accidents, Circulation **9**:719, 1954.
4. Poole, J. L.: Vasocardiac Effects of the Circle of Willis, A.M.A. Arch. Neurol. & Psychiat. **78**:355, 1957.
5. Wakim, K. G., and Fleisher, G. A.: The Effect of Experimental Cerebral Infarction on Transaminase Activity in Serum, Cerebrospinal Fluid, and Infarcted Tissue, Proc. Staff Meet. Mayo Clin. **31**:391, 1956.

Transient Bundle Branch Block Occurring During Slowing of the Heart Beat and Following Gagging

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Latent bundle branch block often becomes manifest when the heart beat is accelerated and reaches a "critical rate."[1] Slowing of the heart action by stimulation of the vagus nerve, on the other hand, is known to abolish bundle branch block.[2,3] In two cases to be reported here transient bundle branch block appeared under unusual circumstances. In one patient spontaneous slowing of the heart beat was consistently followed by aberrant ventricular conduction. In another patient who suffered from paroxysmal supraventricular tachycardia an attempt to stimulate the vagus nerve by gagging was followed by transient bundle branch block.

CASE REPORTS

CASE 1.—R.B., a 57-year-old woman, was treated for hypertensive-arteriosclerotic heart disease in the outpatient department of the Maimonides Hospital. An electrocardiogram on July 31, 1958, showed sinus bradycardia and arrhythmia. While most of the ventricular beats presented the features of normal ventricular conduction, transient bundle branch block appeared whenever the sinus rhythm abruptly slowed down. Fig. 1 shows four strips of the electrocardiogram. The length of the sinus period varies from 1.12 to 1.48 seconds. The P-R interval is constant, measuring 0.20 second in Lead II. It appears that all ventricular beats are produced by stimuli which are transmitted from the atrium. However, those ventricular complexes which conclude the longest cycles show the shape of left bundle branch block. For instance, in Lead I, in which the shortest cycle measures 1.12 seconds, the last beat which terminates a cycle of 1.38 seconds presents the features of left bundle branch block. Similarly, in Lead II the next to the last beat (which comes after a cycle of 1.40 seconds), in Lead III the fourth beat, and in Lead aV_F the fifth beat (both following a sinus period of 1.48 seconds) show the features of aberrant ventricular conduction.

The electrocardiogram from which the four strips of Fig. 1 were taken comprised a total of 153 beats, all of which had a constant P-R interval. Seventeen ventricular beats showed left bundle branch block. In Fig. 2 the ordinate represents the length of the cycles. On the abscissa, increments of the R-R intervals are recorded to the right of the zero point, decrements to the left of it. The beats with normal ventricular conduction are indicated by dots, whereas those presenting aberrant conduction are marked by circles. It can be seen that no ventricular beat which comes after a decrement in cycle length shows the features of bundle branch block. Aberrant

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ventricular conduction occurs only after long cycles which show a marked and usually abrupt increment in duration. Whereas the average cycle length is 1.18 seconds, the period preceding the bundle branch pattern measures on the average 1.38 seconds, with an increment ranging from 0.10 to 0.38 second. This suggests that an increase in vagus tone may be responsible for both the increase in cycle length and disturbance in intraventricular conduction.

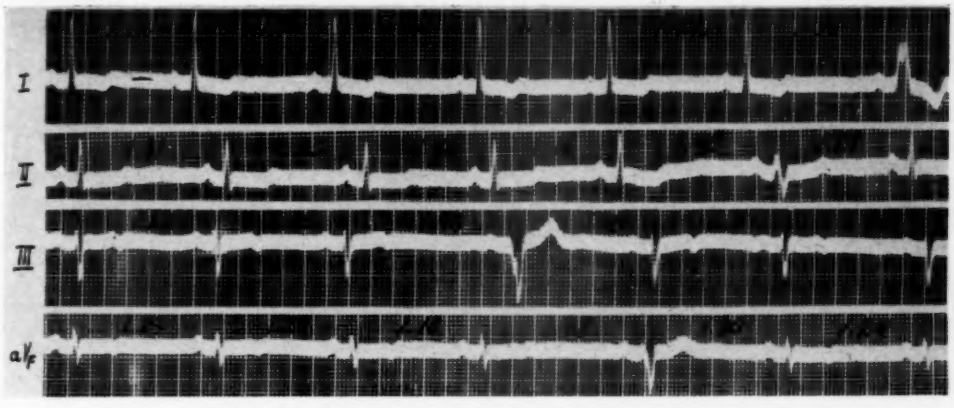

Fig. 1.—Case 1. Sinus arrhythmia and bradycardia. All ventricular beats are apparently caused by sinus excitations. The last beat in Lead I, the next to last in Lead II, the fourth in Lead III, and the fifth in Lead aV_F, all of which follow particularly long cycles, show the signs of bundle branch block.

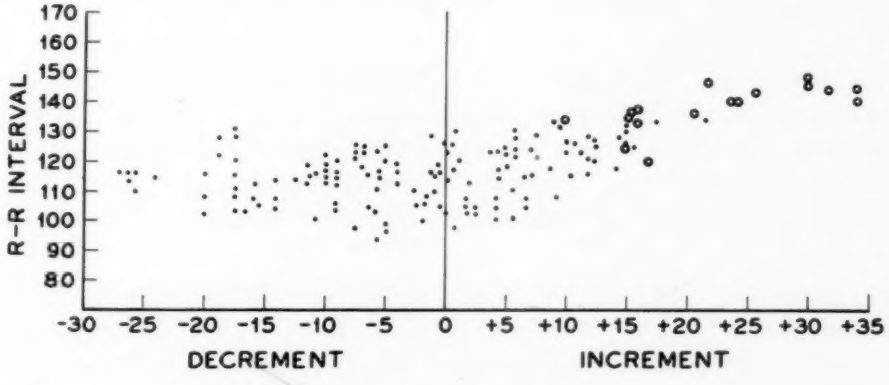

Fig. 2.—Case 1. One hundred fifty-three beats of a single tracing are recorded. The ordinate measures the length of the cycles, the abscissa the decrements and increments of cycle length. The beats with normal ventricular conduction are indicated by dots, whereas those showing bundle branch block are marked by circles. The latter follow the longest cycles with great increments. The numerals stand for hundredths of seconds.

CASE 2.—J.S., a 32-year-old man, suffered from rheumatic heart disease with stenosis of the aortic valve. He had frequent attacks of paroxysmal supraventricular tachycardia, which, as a rule, yielded to carotid sinus pressure.

Fig. 3 illustrates an attack of supraventricular tachycardia. All strips represent Lead II. The upper and middle strips (*A* and *B*) form a continuous tracing. The cycle length ranges from 0.29 to 0.30 second. During the recording of strip *B* an attempt was made to terminate the tachycardia by reflex vagal stimulation caused by gagging. A short pause follows, lasting somewhat less than 1.5 seconds, during which a few beats of bizarre shape appear. Then, the tachycardia is resumed at exactly the previous rate, but the duration of the QRS complex has increased from 0.08 to 0.11 second, and the ventricular beats present the pattern of right bundle branch block.

The identical rate of the tachycardia prior to and after reflex vagal stimulation argues against the view that following gagging a different type of tachycardia developed which is of ventricular origin. In the lowest strip (*C*), which was recorded 2 minutes after *B*, the tachycardia continues with the rate unchanged, but the signs of bundle branch block have disappeared.

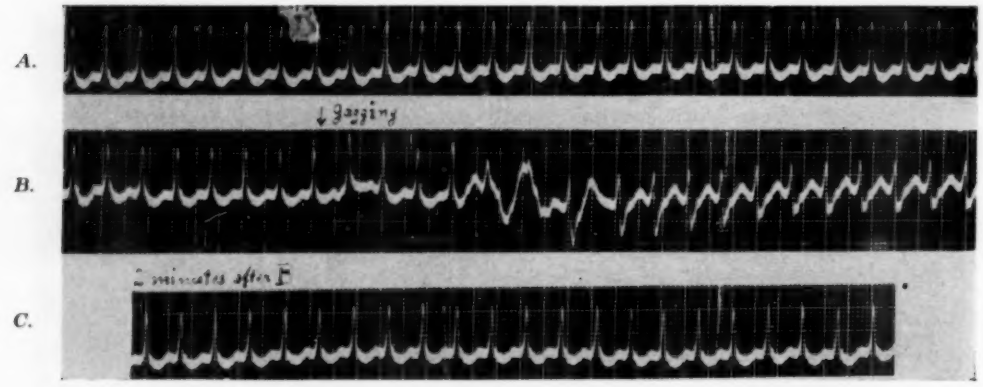

Fig. 3.—Case 2. All strips represent Lead II. *A* and *B* form a continuous tracing. There is a regular paroxysmal tachycardia of supraventricular type with a cycle length of 0.29 to 0.30 second. In strip *B*, gagging is followed by a short pause during which a few beats with bizarre ventricular complexes appear. The tachycardia is then resumed at the previous rate, but the venricular complexes show the features of right bundle branch block. *C* was taken 2 minutes after *B*. The tachycardia continues but the signs of bundle branch block have disappeared.

COMMENT

In the two cases reported here bundle branch block appeared under conditions which suggested the effect of increased vagal tone. In Case 1, left bundle branch block consistently occurred after abrupt increase in the duration of the sinus cycle. In Case 2, an attempt at inhibiting paroxysmal supraventricular tachycardia by gagging was followed by transient occurrence of right bundle branch block.

Experience derived from the experimental animal does not support the view that vagal fibers reach the ventricle of the mammalian heart[4]; nor does stimulation of the vagus nerve, as a rule, affect the ventricle.[5] It is generally known that vagal action does not influence tachycardia of ventricular origin.[6] However, there are exceptions to this rule. Instances are on record in which stimulation of the vagus nerve resulted in abnormal impulse formation or disturbances of conduction within the ventricles.

Piccione and Scherf[7] produced ventricular tachycardia in the experimental animal by applying hypertonic barium chloride or sodium chloride solution to the ventricular surface. When the abnormal rhythm had subsided, stimulation of the vagus nerve caused reappearance of the ventricular tachycardia. Some authors were able to produce paroxysms of ventricular tachycardia by carotid sinus pressure.[8,9] Einthoven and Wieringa[10] produced partial A-V block in the dog's heart by morphine poisoning. Some of the ventricular beats which were clearly of supraventricular origin showed aberrant intraventricular conduction. These abnormalities could be abolished either by section of the vagus or by

atropinization. The authors felt that fibers of the vagus nerve reached the ventricles and directly influenced conduction in the bundle branches when vagal tone was increased by the effect of morphine.

Drury and Mackenzie[11] were unable by stimulation of the vagus nerve in the intact dog to cause disturbances of intraventricular conduction. However, when they damaged a bundle branch and produced temporary disturbance of intraventricular conduction, they were able, after the bundle branch block had subsided, to reproduce it by stimulation of the vagus nerve. The authors offered the explanation that an impulse which passes the A-V node during vagal stimulation suffers a decrement of its strength. Thus, its conduction through the damaged portion of the bundle branch may be impaired. Danielopolu and Danulescu[12] observed that in man suffering from chronic heart disease, latent bundle branch block became manifest upon vagal stimulation. Weiss and Baker,[13] and Comeau and associates[14] published tracings obtained from patients with heart disease, in which transient bundle branch block appeared during pauses in sinus rhythm brought about by carotid sinus pressure.

There are few reports in the literature on observations which were similar to those in our Case 1. Frank Wilson[15] reported a case in which an increase of vagal tone secondary to deep breathing or carotid sinus pressure was accompanied by the appearance of aberrant ventricular complexes. Simultaneously, the pacemaker shifted to the A-V node. Holzmann[16] recorded a tracing in which bundle branch block accompanied the bradycardic phase of a respiratory arrhythmia.

No proof has been brought forward so far that the vagus nerve can exert a direct effect upon the ventricle. The occurrence of abnormal impulse formation and conduction in the ventricle following vagal stimulation can be explained by the assumption that the substance released in the atria during stimulation of the vagus nerve is transported by the blood stream to the ventricle and acts there upon muscle fibers which are sensitized by disease.[16] It is a well-known fact that reflex vagal stimulation exerts a particularly marked effect in patients suffering from coronary arteriosclerosis.

The observation in the two cases of this report allow perhaps an alternative explanation. It is conceivable that vagal stimulation acts by way of a vasoconstrictor effect upon the coronary arteries. Diminution of blood supply might cause disturbance in function of damaged muscle fibers. Thus, latent damage of the bundle branches might become manifest during vagal stimulation. It should be mentioned, however, that the question of constriction of the coronary arteries caused by vagal stimulation is still controversial.[17] In our Case 2, interference with the blood supply could also result from the Valsalva effect of gagging, which causes reduction in cardiac output.

SUMMARY

Two cases are reported in which transient bundle branch block occurred under unusual circumstances which suggested an increase in vagal tone. In an instance of sinus arrhythmia, bundle branch block consistently followed slowing

of the sinus rhythm. In a case of supraventricular tachycardia an attempt to stimulate the vagus nerve by gagging resulted in transient appearance of bundle branch block.

The problem of direct or indirect inhibiting effect by the vagus nerve upon the formation and conduction of impulses in the ventricles is discussed. As an alternative explanation interference with the blood supply is considered to be due either to vagus-mediated constriction of the coronary arteries or to Valsalva effect associated with gagging.

REFERENCES

1. Vesell, H.: Critical Rate in Ventricular Conduction, Am. J. M. Sc. **202**:198, 1941.
2. Freundlich, J.: Über die Beeinflussung Intraventriculaerer Leitungsstoerungen durch den Carotisdruck, Deutsches Arch. f. klin, Med. **168**:360, 1930.
3. Sigler, L. H.: Functional Bundle Branch Block (Partial) Paradoxically Relieved by Vagus Stimulation, Am. J. M. Sc. **185**:211, 1933.
4. Woollard, H. H.: The Innervation of the Heart, J. Anat. **60**:345, 1926.
5. Drury, A. N., and Mackenzie, D. W.: The Influence of Vagal Stimulation Upon Conduction Through the Branches of the A-V Bundle in the Dog, J. Physiol. **80**:329, 1934.
6. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, New York, 1953, Grune & Stratton, Inc., p. 246.
7. Piccione, F. V., and Scherf, D.: The Rhythm Formation of Coupled Beats and Paroxysmal Tachycardia in the Outer Layers of the Myocardium, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **3**:35, 1940.
8. Wenckebach, K. F., and Winterberg, H.: Die Unregelmaessige Herztaetigkeit, Leipzig, 1927, Wilhelm Engelmann, Fig. 190.
9. Meredith, H. C., and Beckwith, J. R.: Development of Ventricular Tachycardia Following Carotid Sinus Stimulation in Paroxysmal Supraventricular Tachycardia, AM. HEART J. **39**:604, 1950.
10. Einthoven, W., and Wieringa, J. H.: Ungleichartige Vaguswirkung auf das Herz electrocardiographisch Untersucht, Pflügers Arch. f. d. ges. Physiol. **149**:48, 1913.
11. Drury, A. N., and Mackenzie, D. W.: Aberrant Ventricular Beats in the Dog During Vagal Stimulation, Quart. J. Exper. Physiol. **24**:237, 1934.
12. Danielopolu, D., and Danulescu, V.: Lesions latentes des branches du faisceau auriculoventriculaire, moyens de les décéler, Arch. mal. coeur **14**:529, 1921.
13. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**:297, 1933.
14. Comeau, W. J., Hamilton, J. B. M., and White, P. D.: Paroxysmal Bundle Branch Block Associated With Heart Disease, AM. HEART J. **15**:276, 1938.
15. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **10**:1008, 1915.
16. Holzmann, M.: Klinische Elektrokardiographie, Ed. 3, Stuttgart, 1955, George Thieme, p. 210.
17. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, Ed. 2, New York, 1955, The Macmillan Company.

Clinical-Pathologic Conference*

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CLINICAL ABSTRACT

History.—The patient was a 59-year-old white divorced cemetery laborer who was admitted to the University of Illinois Research and Educational Hospitals for the fourth, and last, time with a complaint of shortness of breath and "swelling up all over." These complaints had been prominent for three weeks. The patient was reasonably well until age 42, when he developed acute attacks of wheezing and dyspnea, which occurred in the fall for several years. He was told that he had asthma, and treatment was prescribed; but the details are not specified in the record. After several years, the asthmatic attacks decreased in severity. At age 52, about two weeks after surgical repair of a recurrent inguinal hernia, he noted swelling and pain in the right leg. A diagnosis of deep phlebothrombosis of the iliofemoral vein was made in the surgical outpatient department of this hospital, and he was treated with leg elevation and elastic stocking. Because of slight edema of the other leg and complaints of shortness of breath he was referred to the medical clinic. Here the record states that the patient never experienced orthopnea or paroxysmal nocturnal dyspnea. Minimal lung râles and the aforementioned edema were the only abnormal findings described, and a diagnosis of arteriosclerotic and cardiovascular disease with congestive heart failure was made.

ECG exhibited a sinus rhythm with ST and T-wave changes suggestive of myocardial anoxia. He was placed on a low-salt diet; digitalis was administered, and he returned to the clinic for injections of mercury about once every three to four weeks.

He was able to work in the cemetery for six years after the diagnosis of congestive heart failure was made. However, at age 58, in spite of weekly injections of mercury, edema, exertional dyspnea, and abdominal distention became severe, and he was hospitalized on the medical service of this hospital. At this time the blood pressure was 100/80 mm. Hg; pulse was 88 and irregular; and the respirations were 28. He was not orthopneic. There were Grade 1 arteriosclerotic retinopathy, wheezes, and coarse crepitant râles at both lung bases, and dullness to percussion posteriorly at both bases. The heart was enlarged to the left and right by percussion, but no apex impulse was visible or palpable. There were no murmurs, and S_2 at the pulmonic area was louder than S_2 at the aortic area. S_1 at the apex was not accentuated. Cardiac rhythm was irregular, and the neck veins distended when he sat upright. Bulging in the flanks and shifting dullness of the abdomen were present. The liver was felt two fingerbreadths below the right costal margin, and there was extensive edema from the toes to the thorax. The remainder of the examination was not unusual.

The urine exhibited 3-plus protein, with many hyaline and finely granular casts, and a specific gravity of 1.011. Maximal urea clearance was 22 c.c. Hematocrit was 45 per cent; WBC was 6,300, with 81 per cent polymorphonuclear cells, 8 per cent lymphocytes, 8 per cent monocytes,

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2 per cent eosinophils, and 1 per cent basophils. Serologic test for syphilis was negative. Nonprotein nitrogen was 50 mg. per cent; albumin, 3.7 Gm. per cent; globulin, 2.4 Gm. per cent; and serum electrolytes were within normal limits. Several stool examinations and cultures revealed *Endamoeba histolytica* cysts and trophozoites. Sputum smears and cultures showed no acid-fast organisms. The basal metabolic rate was —5 per cent.

X-rays and kymograms of the chest were taken and will be described below. ECG showed auricular fibrillation and tendency toward low voltage. Renal biopsy was compatible with arteriolar nephrosclerosis.

On bed rest, low-salt diet, and improved digitalization, he rapidly lost all edema fluid. One gram of oral quinidine sufficed to revert his rhythm, and the latter was maintained by administration of 200 mg. of quinidine twice daily.

He was discharged on the same cardiac regimen, and the amebiasis was treated with apparent success in the outpatient department. In the last year of his life he was admitted three times to this hospital. One admission was necessitated because of either recurrence or relapse of amebiasis, successfully treated with carbarsone and emetine; and the final two admissions, by a return of exertional dyspnea and marked edema occurring in spite of the cardiac regimen to which he adhered.

Alcoholic intake and diet are not described in the record.

Physical Examination.—At the time of the final hospitalization the following signs were present: the blood pressure was 85/65 mm. Hg, pulse was 60 and regular, and respirations 24 per minute, with a temperature of 98.8° F. There was pitting edema to the rib cage. The chest was hyperresonant, and there were dry crackling râles in both bases. The heart was not described as enlarged; rhythm was regular; heart tones, faint; and no murmurs were audible. Neck vein distention, ascites, and hepatomegaly were present. The remainder of the examination revealed no major abnormalities.

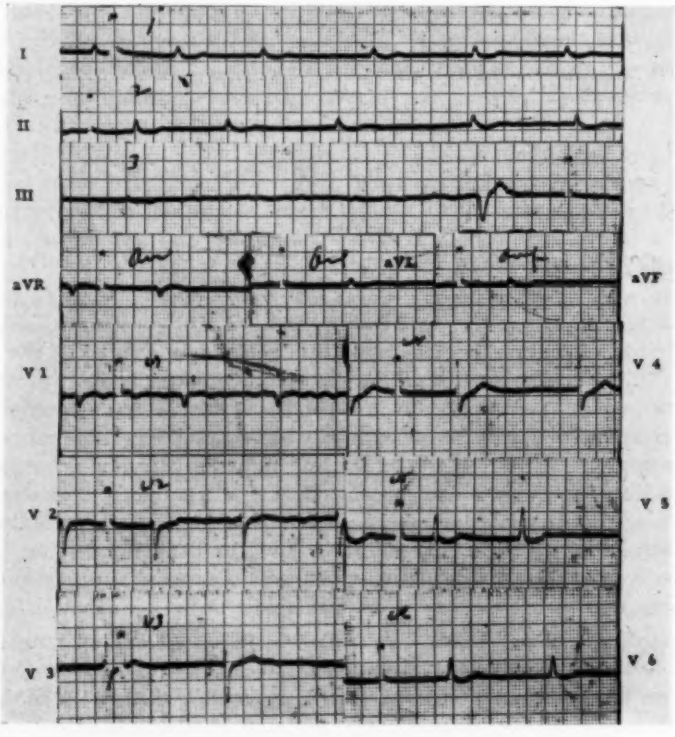

Fig. 1.—Electrocardiogram similar to many others, showing atrial fibrillation with a slow ventricular rate, low voltage of QRS deflections, and ST-T abnormalities; the latter were suggestive of digitalis effect.

Laboratory Data.—Urinalysis showed a specific gravity of 1.000, 1-plus albumin, 1-4 WBC per high-power field, and many granular casts. Phenolsulfonphthalein excretion was 6 per cent in three hours. Hemoglobin was 11 Gm.; hematocrit, 41 per cent; WBC, 12,000 with a normal differential. Albumin 2.7, globulin 1.5 Gm. per cent, nonprotein nitrogen 96 mg. per cent. Electrolytes were normal except for a CO_2 combining power of 15. More chest x-rays were obtained. ECG (Fig. 1) showed atrial fibrillation with a slow ventricular rate, low voltage of the QRS deflection, and ST-T abnormalities. The latter were suggestive of digitalis effect. Circulation time A to L was 7 seconds; A to T, 80 seconds.

Hospital Course.—The patient was placed on bed rest; digitalis dosage was increased; and ammonium chloride and Diamox, followed by mercury, were administered. Loss of weight was minimal, and after three weeks be began vomiting. Tube feedings with added salt were administered, but he rapidly gained 14 pounds. Throughout this time, his Na and Cl fell gradually to 121 and 86 mEq./L. Southey tubes were inserted in both ankles, with a loss of 20 pounds. As a final attempt at electrolyte regulation, intravenous dextrose was given, but proved useless. Terminally, the patient vomited and aspirated; urine output ceased, and nonprotein nitrogen rose to 104 mg. per cent.

DISCUSSION

DR. HARVEY: This man had a large number of chest films over a period of five years, and they always showed fairly prominent cardiac enlargement—but then it was general in type. There was no specific predominance of one chamber over the other (Fig. 2). He always showed a minimal degree of congestion, but it varied slightly from time to time; and, further, at various times

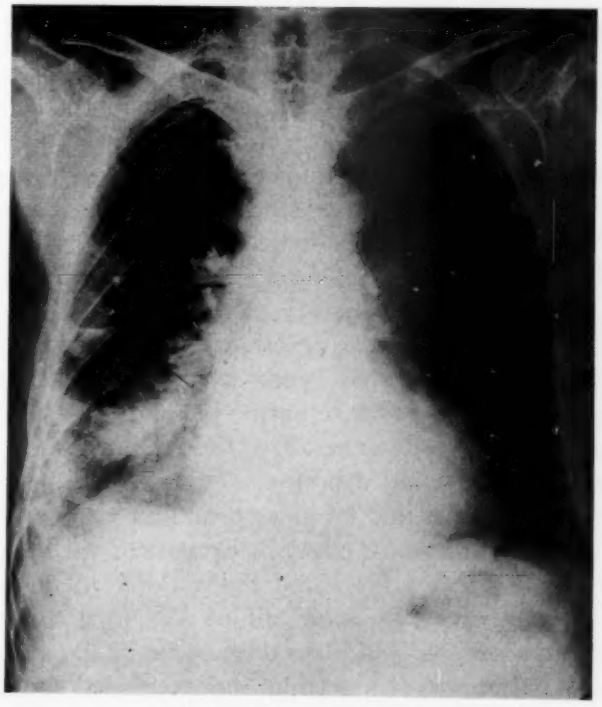

Fig. 2.—X-ray of chest, showing the following: the heart is slightly enlarged, and there are pleural scarring and small fluid accumulations on the right. Density in the lower right lung is due to pleural change.

he showed effusion, chiefly on the right side. We have two lateral chest films of him, and they show no striking prominence of any one ventricle but some prominence of all chambers. At times, he would show a density which we would have liked to make out as an infarct; but then it never started the way an infarct does, and the lateral studies showed that it was a collection of fluid in the interlobar region. Barium-swallow studies showed no significant displacement of the esophagus.

Any one-centimeter area you take of the heart border on kymographic study shows these fairly distinct pulsations, diastolic and systolic, so that the myocardium was contracting with a fairly uniform intensity, not as irregular as you might see in fibrillation. There were fairly good shock-like pulsations transmitted into the aortic wall as well.

I failed to mention that on some of the lateral films there was a little blunting of the posterior cardiophrenic angle, with a small pericardial effusion, but it was small.

In connection with the intravenous renal dye studies, we never saw enough density for diagnosis; therefore, as a result, they were rather disappointing. Even in the 60-minute film which I have, there was no significant collection of dye density in the bladder; and consequently we would not expect any detail in the internal kidney. Therefore, he had suppressed renal function.

In summary, he had a consistent and constant cardiac enlargement, generalized in character, with some left ventricular prominence, variable degrees of pulmonary congestion, and mainly right pleural effusion with nonvisualization of dye excretion from the upper urinary tract.

DR. GRAETTINGER: The patient apparently was quite well until he was 42 and then began to get curious attacks of asthma in the fall. He then went along for another 10 years without any difficulty until, after herniorrhaphy, some observers felt that congestive failure was present because of the fact that he had some edema. Apparently this was not very severe, because he was able to continue his work in a cemetery for some time without any treatment. When he was 58, he came into the hospital with signs of fluid accumulation, pleural effusion bilaterally, and without a history of serious dyspnea. At this point we find a serious discrepancy in the history of this patient from the histories usually given by patients with the common types of heart disease, since it becomes evident that he had had edema and retention of fluid out of proportion to pulmonary symptoms; in other words, generalized fluid retention was more prominent in his history than was exertional dyspnea.

At this point, I think it would be most profitable to spend a few moments considering the abnormalities which could be present in the heart to account for this unusual history. In Table I are listed the majority of disorders which can cause the clinical syndrome of congestive failure. We must consider those lesions which can cause edema, ascites, and pleural effusions in the absence of a history of episodes of acute pulmonary congestion and exertional dyspnea. In the first category in the Table are those lesions in which myocardial inadequacy, i.e., an inadequate cardiac output, develops from primary involvement of the myocardium. Rheumatic myocarditis, other myocarditides, and the various myo-

cardiopathies all should be mentioned, since they cause total myocardial inadequacy without a discrepancy between involvement of the left and right ventricles leading to pulmonary congestion. We have no history here to suggest any one of these disorders. Ischemic myocardiopathy, coronary artery disease, ordinarily involves the left ventricle and, hence, results in a story of pulmonary congestion when it produces congestive failure. Furthermore, in the absence of a history of angina pectoris or evidence for myocardial infarction this diagnosis cannot be made.

The second great class of lesions which produce myocardial inadequacy loads the myocardium either by imposing an excessive amount of pressure work on the heart muscle or by an inordinate amount of volume work. Under the category of pressure loads, most of the lesions affect the left ventricle primarily, and, hence, failure is accompanied by pulmonary symptoms; we have no evidence for systemic hypertensive disease or valvular stenoses. Pulmonary hypertension, however, must seriously be considered, since this is a disorder which places a pressure load on the right ventricle and may cause an inadequate cardiac output, with consequent fluid accumulation without accumulation of fluid in the lungs. We shall return to this possibility subsequently.

We have no evidence for valvular regurgitations, left-to-right shunts, or patent ductus arteriosus, which comprise lesions which place volume loads on the ventricles and may cause failure without disproportionate pulmonary symptoms.

TABLE I

Myocardial Inadequacy	*Circulatory Demand*
1. Primary:	Exercise
Rheumatic myocarditis	Fever
Ischemic myocardiopathy	Anemia
Other myocarditides	Pregnancy
Myocardiopathies	Thyrotoxicosis
Amyloid, etc.	A-V fistula
	Beriberi
2. Secondary:	
A. Pressure loads:	
Systemic hypertension	
Pulmonary hypertension	
Aortic stenosis	
Pulmonic stenosis	
Mitral stenosis	
B. Volume loads:	
Valvular regurgitation	
Left-to-right shunts	
Patent ductus arteriosus	
3. Filling Abnormalities:	
Tricuspid stenosis	
Constrictive pericarditis—tamponade	
Endocardial sclerosis	
Arrhythmias	

The third category of abnormalities which can cause myocardial inadequacy is that in which filling of the heart is impaired and, hence, cardiac output is compromised. These abnormalities may cause the kind of history presented by this patient. We have no evidence for arrhythmias or tricuspid stenosis in this patient. However, restriction of filling of the heart by pericardial constriction must be considered.

Relative myocardial inadequacy can also occur when the demand for cardiac output exceeds the capability of the heart to pump blood; and, indeed, under certain circumstances even the healthy heart can fail under conditions of excessive circulatory demand. Pulmonary symptoms are often mild, even in the presence of marked fluid accumulation. We have no evidence in this patient of any of the disorders listed under circulatory demand in the Table.

In our patient, with a history of chronic, progressive fluid retention with minimal pulmonary symptoms, I would suggest therefore that myocardial inadequacy secondary to the pressure load imposed by pulmonary hypertension or myocardial inadequacy consequent to the filling abnormality imposed by constrictive pericarditis are the most likely possibilities. With regard to the latter possibility we have no etiology for pericarditis. We are told, however, that no impulse was palpable or visible on examination. On his first visit, it is said that his heart was enlarged, and on the second visit, that it was not enlarged. The occurrence of atrial fibrillation is a point in favor of considering pericarditis. This arrhythmia occurs with some frequency in pericarditis and can often easily be converted, as was the case in this patient, with relatively small doses of quinidine. With regard to the former possibility, pulmonary hypertension, various disorders may cause this. Although this patient had asthma and may have had emphysema, from the clinical description, cor pulmonale in cases of asthma and emphysema is most often preceded by serious respiratory difficulty, with the occurrence of arterial unsaturation and consequent polycythemia, which are not present here. We have no etiology for pulmonary fibrosis. We have in this patient, however, a possible etiology for pulmonary hypertension, in the form of multiple pulmonary emboli arising from thrombi in the veins of the leg. I would, therefore, suggest that multiple pulmonary emboli with myocardial inadequacy secondary to the pressure load imposed by pulmonary hypertension is the most reasonable diagnosis in this patient, with chronic cardiac constriction being the next most likely diagnosis.

DR. PAUL: Dr. Graettinger has given us a very nice background of almost all the possibilities, but then perhaps there are one or two more that might be mentioned; and there are one or two additional matters which I would also like to mention in the time allowed me.

I would agree that the history of asthma, which was initially described in the records, is probably unrelated to his terminal illness. We have really only two clues to etiology in connection with his history, it seems to me: the thrombophlebitis and the amebiasis; and both of these might conceivably have had something to do with his terminal illness. It is interesting that, as in this case, so often the diagnosis of coronary heart disease is made purely on the basis of advanced age. It is also interesting in this case that there is no mention of the

individual's ever having received oxygen, suggesting that the pulmonary symptoms were not of remarkable importance, at least as they were observed.

Now, I would like to make one comment regarding the absence of a left-sided lesion. I think that the history does not suggest an isolated lesion of the left side of the heart or even a past history of hypertension, and a process primarily involving the left side would be unusual. I would like to comment, however, that there are exceptions to this. I can think of the patient, for example, who had a tight mitral valve, a tight mitral stenosis, who was able to lie flat just as easily as if he were on that table, whose symptoms were entirely those of the right side of the heart, and who succumbed and at autopsy had a tricuspid lesion plus a very tight mitral valve. Occasionally we see this. There occasionally are patients who have some bypassing of the lungs as far as symptoms are concerned, even though the primary lesion is on the left. However, this is unlikely here.

Coming to the first diagnosis that Dr. Graettinger mentioned, this is an attractive diagnosis in many ways. However, this is a diagnosis that is rather difficult to make. The occurrence of multiple pulmonary emboli, leading to a cor pulmonale, congestive failure, and death, is unfortunately one which presents serious diagnostic difficulties. These patients often have no classic history of pulmonary infarcts—they do not cough up blood often, and x-ray findings typical of infarction are absent.

I would have liked to have some additional clues in regard to this patient. For instance, I would have felt much happier if the x-rays which were shown us had shown some increasing size or greater prominence of the main pulmonary artery or a cutting off of the right or left pulmonary artery, such as is sometimes seen when there has been an occlusion distant to it. It did not seem that this was very apparent. I would have felt much happier if this patient had developed electrocardiographic evidences of some right-sided lesion, with right ventricular hypertrophy or even incomplete right bundle branch block. However, these are not here. I do not believe that fibrillation is common with multiple emboli; but, then, it can occur in a variety of conditions. Therefore, there are some factors that disturb me with the diagnosis of a cor pulmonale.

There is one fact in this history which is interesting, and it is that from the very outset the patient had a very narrow pulse pressure. You will find that when he came in, at the age of 58, he had a blood pressure of 100/80 mm. Hg, and that subsequently the blood pressure was 85/65 mm. Hg. I also think that there is another one in the record which is very narrow. By the time this blood pressure reading was taken, he had a very low cardiac output; and regardless of what the x-rays showed, I would think that he must have had a tired and weak myocardium or some factor limiting it.

The factors that could produce this include myocarditis and constrictive pericarditis, which have been mentioned, amyloidosis, endocardial sclerosis, and, in rare cases, thrombosis of the endocardial surfaces of one or both ventricles, of unknown origin, not necessarily involving the valves. There is enough here to suggest one of these diagnoses. As much as I am tempted to follow along with the diagnosis of multiple pulmonary emboli, I am distressed that a man who had this for seven years never developed better x-ray or ECG evidence of cor pul-

monale. Against constrictive pericarditis is the absence at the end of seven years of any calcification of the pericardium, and there is also the fact that we do not have evidence of tuberculous infection or of any old scars in the lungs. Furthermore, I am not aware that primary amyloid disease involving the myocardium goes for as long as seven years. It may, but I have not seen it go on for that long. The cases I am familiar with have given symptoms over shorter periods of time.

Endocardial sclerosis, or thrombosis of the endocardial surfaces, can produce a somewhat similar picture. I am going to vary from Dr. Graettinger's diagnosis of pulmonary emboli, which is statistically best to make, and suggest to you that on the basis of the evidence of a rather markedly reduced cardiac output, which evidently was present over a considerable time—in the absence of evidence of hypertension and coronary disease—this patient had a process primarily limiting his myocardium, and that just possibly this could involve the endocardium.

QUESTION: You did not mention this circulation time of 7 and 80 seconds. What part do you think that this plays in it?

DR. PAUL: Frankly, I doubt if that is correct. This is an extremely marked discrepancy in the patient who, at the time of his terminal illness, presented a picture of congestive failure—a failure of the left side, with a failure on the right side, and venous hypertension. It would be difficult for me to believe that his right ventricle had such a small chamber, that the mixing was so perfect that a time of 7 seconds was actually obtained, and that the process in the left side was so advanced that an 80-second termination was correct. I would wonder whether the patient was able to give a precise end-point. If I were to get that type of reaction, I would question whether that was correct.

DR. KRAKOWER: He was a well-developed individual, in fact, measuring a little over six feet in height and weighing about 140 pounds. There was considerable edema of the lower extremities and sacral region but none above that level. When we opened the cavities, we found that he had extensive pleural adhesions on both sides, particularly marked on the right, with very marked pleural thickening. He had about 100 c.c. of clear, straw-colored fluid in the pericardial sac and, in addition, 100 c.c. of clear fluid in the peritoneal cavity.

The heart weighed 380 grams. The right atrium was markedly dilated and hypertrophied, with a mural thrombus in the appendage, measuring 4 by 2.2 by 1 cm. (Fig. 3). There was a systolic pocket in the mural endocardium 1 to 1.5 cm. below the mural thrombus and 3 mm. in depth. The tricuspid ring was dilated up to 14 cm. in circumference, but its valve was not remarkable. The right ventricle was exceedingly small, with a myocardium measuring from 0.3 to 0.8 cm. in thickness. There was marked endocardial thickening, involving the inflow tract of the small right ventricle, including its papillary muscles. The pulmonary valve and ring were not remarkable, measuring 8.5 cm. in circumference.

The left atrium was greatly dilated, with slight opaque thickening of its endocardium. The mitral ring was 12 cm. in circumference, and its valvular leaflets were not abnormal. The left ventricle was again a mere appendage to the very large auricle (Fig. 4). Its small chamber presented a firm, brownish-red myocardium, varying from 1 to 1.5 cm. in thickness, with scarring of the myo-

Fig. 3.—View of the right side of the heart, showing the very large right auricle and the thrombus in the appendage. The small right ventricle with endocardial thickening is clearly apparent.

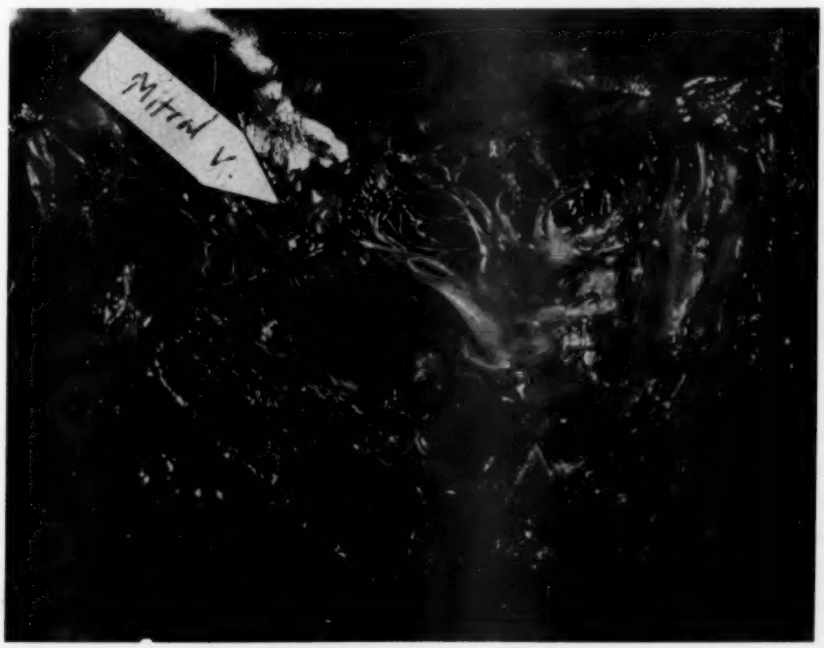

Fig. 4.—View of the left side of the heart, showing endocardial thickening along the inflow tract. The irregularity and grooved appearance of the apical portion of the left ventricle represent the site of a compact, thick hyaline thrombus.

cardium in the apical region. The inflow tract of the ventricle presented a very thick, opaque endocardium, with a large superimposed laminated thrombus in the inferior third to half of the chamber. The endocardium of the outflow tract on the left side was relatively normal.

The aortic valve was essentially normal, and the circumference of its ring was 8.0 cm. The coronary arteries were widely patent, with minimal atherosclerosis. The aorta was moderately dilated in its ascending arch and thoracic portions, with, in general, little atherosclerosis. The abdominal aorta, however, presented a moderate amount of atherosclerosis.

The thickened endocardium differed microscopically in its content of fibrous and elastic tissue in different areas (Fig. 5). There was abundant fibrous and elastic tissue in some areas, presenting the appearance of an acceptable fibroelastosis. In other areas, there was little elastic tissue and abundant fibrous tissue which might or might not be supplied by a vascular bed, the pattern of which was that of an older granulation tissue. This latter occurred with or without the superposition of a more clearly recognizable deposition of hyalinized fibrin. Furthermore, the thickened endocardium either presented a fairly regular border in its contact with the myocardium or the fibrosis extended irregularly into the myocardium.

The right lung weighed 1,160 grams. There was a markedly thickened visceral pleura, varying from 1.0 to 8.0 mm. in thickness. The right pulmonary artery and its branches were filled with loose thromboembolic material. The lung on section was somewhat granular, and some fluid could be expressed from it. The left lung weighed 670 grams. The medium-sized branches of its pulmonary artery contained unattached, recent thromboemboli. Its cut surfaces resembled those of the right. There were no gross infarcts in either lung. The tracheobronchial tree contained sanguinopurulent exudate, and its mucosa was reddened and granular. Microscopically, the lungs presented marked changes of chronic passive congestion, with only a modest amount of edema but with early foci of bronchopneumonia, and areas of older organizing pneumonia. There were none of the changes usually encountered in classic asthma and no appreciable degree of emphysema. However, there were thickening and fibrosis of the small pulmonary arterial vessels. The spleen, weighing 290 grams, revealed a 4-cm. area at its upper pole where the capsule was markedly thickened (2.0 to 2.5 mm.). There was a single depressed, old infarcted area at the lower pole. Microscopically, there were changes of chronic passive congestion in the spleen in areas other than the infarct. The liver (1,210 grams), firm and pale, showed a chronic perihepatitis with adhesions to the diaphragm. In addition, there was a modest degree of chronic passive congestion but with irregular attempts at portal lobulation. There was an associated, unusually heavy lymphocytic infiltration of the portal spaces microscopically. In effect, there was a mild cirrhosis of the liver, not clearly cardiac. The walls of the hepatic veins and the inferior vena cava were thickened. The kidneys (each 100 grams) presented adherent capsules with granularity of the surface. The cortex was thinned to 3.0 to 5.0 mm. Microscopically, there were cortical scarring and marked interstitial medullary fibrous thickening. Subscapsularly, there were cellular infiltrates with periglomerular fibrosis and tubular atrophy. There were marked hydropic changes in the tubular

epithelium of the better-preserved nephrons. It was difficult to determine to what extent these changes represented an older chronic pyelonephritis or "cyanotic" atrophy on a vascular basis. There was no evidence of amebiasis. There were, however, patches of melanosis of the colon and diverticula of the sigmoid colon. There was an acute and chronic prostatitis. In the brain, despite relatively little gross atherosclerosis of the basilar vessels, there were two softenings, both in the frontal region of the left cerebral hemisphere.

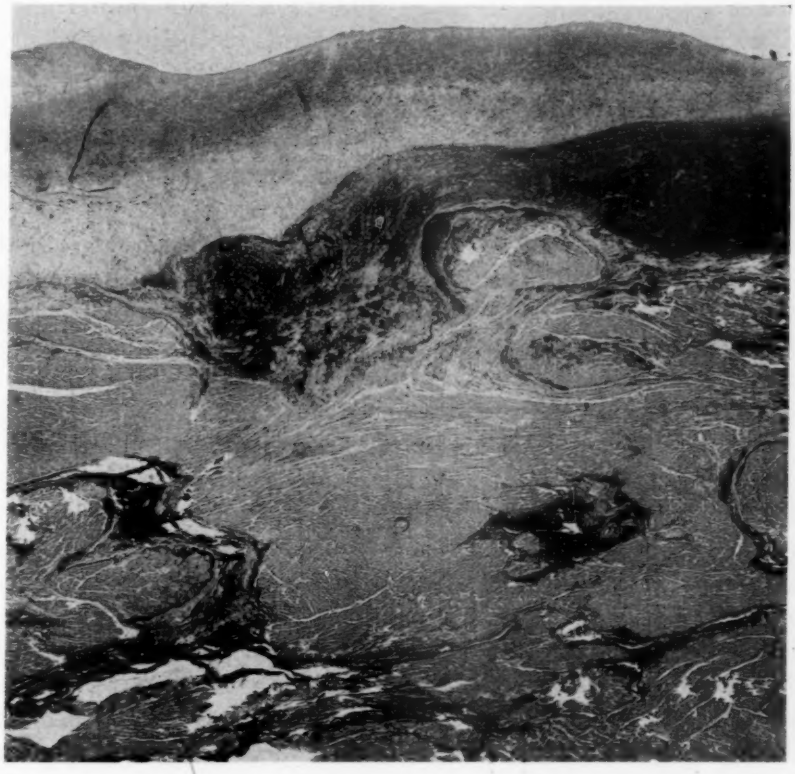

Fig. 5.—A microscopic view of the endocardium with avascular fibroelastic thickening toward the right and vascularized fibrosis toward the left. (Weigert-Van Gieson stain; ×15, reduced ⅙.)

In essence, therefore, we are dealing with a combination of endocardial fibroelastosis and fibrosis, with or without thrombotic organization of very small right and left ventricles. One could in this instance properly regard the changes in the endocardium as being constrictive, limiting the diastolic expansion of the ventricles. Surely, their capacity at the time of death seemed inadequate to have maintained a near-normal cardiac output. The auricles, by contrast, were very large, serving in a sense as storage cisterns. There were, as might be expected, changes of visceral passive congestion. There were, however, changes which could not be so readily explained. The reason for the serosal thickenings of the pleura on the right and liver and spleen is not clear, except as it may be related to repeated serous effusions. The etiologic basis for the fibrosis of liver

and kidney is likewise not too apparent. The immediate cause of death was due to rather massive pulmonary embolism, the source of which might have been the mural thrombus in the right auricle. The vessels of the extremities were not examined to exclude those as a possible source of the emboli. The cerebral softenings and the single splenic infarct probably represent embolic phenomena from the mural thrombus in the left ventricle.

It is impossible to enter into an extensive discussion of the pathogenesis of endocardial sclerosis. The present case offers no support for the acquired variants, as is seen with subendocardial infarction, hemodynamic disturbances associated with valvular deformities, or the more recently described forms of endomyocardial necrosis and fibrosis occurring in East Africa. There is some support for the view that one is dealing here with a so-called congenital variant. Recently, Thomas, Randall, Bland, and Castleman (New England Journal of Medicine 251: 327, 1954) have described such infantile, childhood, and adult types. Various reasons have been set forth to explain the so-called congenital forms of endocardial thickening, viz.: (1) intrauterine endocarditis; (2) anomalous development of the endocardium in conjunction with other abnormalities of the heart and great vessels; (3) the result of primary myocardial hypertrophy; (4) the result of abnormal hemodynamic and hemochemical processes; (5) the result of subendocardial myocardial degeneration; (6) a form of collagen disease; (7) the result of progressive organization of repeated deposits of fibrin; (8) the result of endocardial anoxia, as seen with intrauterine closure of the foramen ovale, or an anomalous origin of a coronary artery from the pulmonary artery; (9) primary cardiac muscular weakness.

Whatever might be the initial cause of this endocardial sclerosis, one thing seems clear from the present case: that superimposed thrombosis with subsequent organization plays an important role in the further thickening of the endocardium, and with it the possibility of a constrictive effect serving to limit or diminish the diastolic size of the ventricular chambers. That this possibility exists is indicated by the fact that this patient in the earlier stages of the disease presented an enlarged heart, the usual finding at autopsy in these cases of endocardial fibroelastosis, particularly as it relates to the affected ventricles; yet in the final admission, at least clinically and at autopsy, there was no such enlargement.

Diagnosis: Fibroelastosis of the Heart in an Adult

Review

Muscular Contraction*

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In recent years there have been considerable advances in our knowledge and understanding of the mechanism of muscular contraction. These have come from two main sources—from biophysical and biochemical studies of purified muscle proteins and of "model" muscle systems of various types, and from investigations of the molecular structure of muscle and the changes in that structure which occur during contraction. The large-scale physiological properties of muscle are now beginning to find expression in structural and chemical terms.

Muscle may be considered as essentially a highly specialized machine, constructed from organic materials, which utilizes chemically stored energy and performs mechanical work. The existence of some such mechanism is indispensable to the directed movement of any biological system, and its speed and efficiency decisively influence the types of animal life which can exist. All machines arouse our curiosity, and this one is no exception; the question of how it works comes at once into our minds. This article will not answer this question, but it will attempt to summarize some of the evidence and arguments on which our present ideas about muscular contraction are based. These ideas, though fruitful in many respects, have one very great failing: they have not enabled us to decide what fundamental principle or property is involved in contraction. Non-biologists may be surprised that such an unsatisfactory state of affairs should prevail in so important a subject, but, in fact, our knowledge and understanding of muscle are probably more complete than they are of any other biological system. If the mystery of contraction remains unsolved for long, it will not be for want of experiment or thought.

GENERAL PROPERTIES OF MUSCLE

There are basically two different types of muscle. Voluntary muscles are quick-acting and exhibit a banded or striated appearance in the light microscope; this class includes the skeletal muscles used to produce body and limb movements in

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vertebrates. Involuntary muscles, such as those which produce intestinal movements, or the dilatation of the capillaries, are in general much slower in their operation, and they do not appear banded. The two types are usually referred to as "striated" and "smooth" muscle, respectively. Cardiac muscle seems to occupy an intermediate position, for although not under voluntary control, its structure resembles that of striated muscle. The properties of smooth muscle have been studied a good deal less than those of striated muscle, and it is with the latter that we shall mainly be concerned.

A whole muscle is built up of a large number of individual fibers, which range in diameter from 0.01 to 0.1 mm., and which may extend the whole length of the muscle. These fibers are electrically excitable, and they will contract when an electrical impulse is transmitted to them down the motor nerve. A single impulse produces a single contractile event, known as a twitch, whose duration is of the general order of magnitude of one tenth of a second, although considerable variation exists between different muscles. A longer contraction, known as a tetanus, can be maintained by a continuous flow of impulses. When the impulses cease, contraction ceases too, and if the muscle has been allowed to shorten it may be re-extended by a very small force. The muscle is said to relax. Under normal physiological conditions muscles do not in general shorten to below 65 per cent of their resting length, nor stretch to more than about 140 per cent of their resting length. The normal range of operation is often even more restricted than this: 85 per cent to 120 per cent would be a typical figure. The tension exerted by a muscle is a maximum at resting length and decreases on either side of that length.

During a tetanus, a muscle can exert a tension of about 4 to 5 Kg. per square centimeter of its cross section. The tension exerted is a function of the velocity of shortening.[1] Maximum tension is exerted when the muscle is not allowed to shorten at all, i.e., during an isometric contraction. If P_o is the maximum tension that the muscle can exert at any particular length, then when it is shortening with velocity v the tension exerted will be P, where $(P + a)\, v = (P_o - P)\, b$, a and b being constants for a given muscle. This is the well-known Hill equation. One feels that such a simple relationship must reflect some very simple feature of the mechanism of contraction.

HEAT PRODUCTION

When one considers the production of heat by a contracting muscle, the above relationship takes on an even simpler form. The heat given out by a muscle during contraction may conveniently be divided into two parts: the initial heat, which always appears, whether the muscle is allowed to shorten or not; and the shortening heat, which appears when the muscle decreases in length.[2] No heat changes take place when the muscle relaxes and returns to its resting length. The amount of shortening heat is proportional to the distance the muscle shortens, and is independent of the tension being exerted during the shortening process. Moreover, the heat evolved for an amount of shortening x is found to be equal to ax, where the constant a has the same value as it does in the force-velocity equation. Thus, leaving aside the initial heat, the left-hand side of the

force-velocity equation given above will represent the total rate of energy release (heat + work) by the contracting muscle. The equation therefore shows that this quantity is proportional to the difference between the maximum tension and the tension which is actually being exerted. This seems to be a very significant relationship.

ENERGY RELEASE

The fact that the amount of heat produced when a muscle shortens by a given distance is independent of the external work done by the muscle is most remarkable. A good many of the more straightforward mechanisms that might be suggested for contraction set free a constant total amount of energy when they shorten a given distance, and they would therefore predict a heat of shortening which increased as the external work decreased. But in muscle the total energy released in a given distance varies with the load, and it is always equal to the external work done plus a constant shortening heat. Moreover, this is an inherent property of the contractile material, and is not dependent on some feedback arrangement in the nervous system. In some respects the system resembles an electric motor drawing a larger current from the mains supply when its speed is decreased by an external load, although this analogy cannot be pursued very far.

The mechanism of contraction must clearly be of a very special kind. First of all, the chemical reaction which releases energy for contraction must be linked to a movement or change of shape in the molecular structure of the muscle. Secondly, this movement or change of shape must enable the muscle as a whole to shorten by at least one third of its resting length. Thirdly, the amount of reaction which takes place must be determined by the external work done by the muscle and not by the distance it shortens. Fourthly, the mechanism must give the very simple force-velocity relation described by the Hill equation. Fifthly, after a contraction the muscle must be able to return to its resting length without any further heat changes taking place. Thus, even apart from its relevance to muscular contraction, it is of considerable intrinsic interest to try to discover how such a molecular mechanism can work.

APPROACHES TO THE PROBLEM

The properties of muscle which have been briefly outlined above are so striking and so clearly defined that one feels they ought to be explicable in fairly simple terms. An explanation can be sought in two rather different ways. The first approach is simply to try to see how a muscle is constructed. The large-scale structures can be studied in the light microscope; the details of the fine structure can be observed in the electron microscope or investigated by x-ray diffraction techniques. If the structure of the working parts of a muscle can be described in sufficient detail, then one should be very close to understanding how the mechanism operates.

The second approach is the biochemical one. Many of the components of a muscle can be extracted and purified, and their chemical and physical properties studied either individually or in combination with one or more other components.

Systems can be set up—for instance, artificial fibers prepared from purified muscle proteins—which display some of the properties of living muscle, and whose behavior can be studied under much more closely controlled conditions.

The two approaches can never be wholly separate, nor should they be; they differ much more in the way the information is obtained than in the type of information they ultimately seek. The correlation of the information obtained by the different methods not only helps to preserve an atmosphere of realism in the different disciplines but should eventually remove the boundaries between them, so that the same phenomena might equally well be described by a physiologist, a biochemist, or a physicist, each using terms which have a real meaning to the others. Before discussing the contractile structure itself, however, brief mention should be made of the means by which the signal for contraction is transmitted into that structure.

MECHANISM OF STIMULATION

The muscle fiber is the smallest unit which will perform a normal physiological contraction. Each fiber is surrounded by a thin membrane which is electrically polarized and in the resting state has a potential difference of about one tenth of a volt across it, the inside being negative. When the muscle is stimulated, via its motor nerve and motor end-plate, a wave of depolarization, the action potential, travels down the muscle membrane, with the result that the potential difference across it falls to zero and, in fact, overswings and reverses in sign. Almost immediately the muscle contracts. The depolarization of the membrane is known to alter its permeability to different ions, and it is natural to inquire whether the passage of some specific ion through the external membrane could trigger off the contraction. However, such an explanation is not tenable, at least in its simple form, for the muscle fiber becomes fully active across its entire cross section in a much shorter time than such ions would take to diffuse to or from the center of the fiber.[3] Recently, it has been suggested[4] that the signal for contraction might be transmitted into the interior of the fiber at the requisite speed as a wave of depolarization in an internal transverse membrane. A system of such transverse membranes, spaced at short intervals along the fiber, and each releasing activator in the interior of the fiber when they were depolarized, would then provide the necessary speed of activation. Strong evidence has been produced[4] that such a mechanism does in fact exist in striated muscle.

THE CONTRACTILE STRUCTURE

The contractile material is located inside the muscle fibers in the form of thin longitudinal fibrils, called myofibrils, about 1 micron in diameter, packed close together across the width of the fiber and extending along its whole length. If the fibers are disrupted mechanically, for instance in a Waring blender, the individual fibrils are released. These isolated myofibrils provide a very important experimental material. Though they cannot, of course, be stimulated electrically, they can be made to contract by appropriate biochemical treatments; they seem to contain the essential contractile apparatus of muscle, still in a highly organized

form, but free from the complicated and uncontrollable factors present in a whole living muscle.

The fibers of voluntary muscle are crossed by a regularly repeating pattern of bands; these cross-striations have a periodicity of the order of 2 or 3 microns at resting length. The period seems to be constant for a given type of muscle at resting length, but varies somewhat from one type of muscle to another; some muscles (e.g., the leg muscles of certain spiders) have exceptionally long striations.

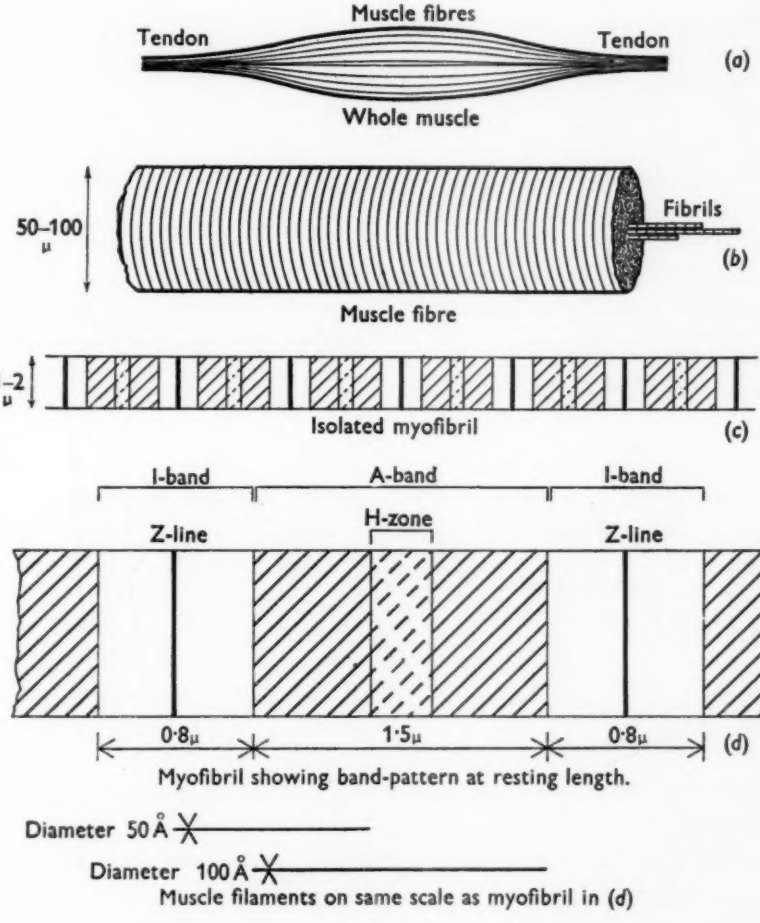


Fig. 1.—The structure of muscle at different levels of organization; dimensions shown are those for rabbit psoas muscle.

This banding is a property of the myofibrils, which are arranged in the fiber with their striations in register. The pattern is shown in Fig. 1, and Fig. 3,*A* shows an individual myofibril photographed in phase-contrast illumination. The principal feature is the succession of alternating dark and light bands, which correspond to dense and less dense regions of the myofibril The dense bands are birefringent and are known as the A (anisotropic) bands; the less dense bands are relatively nonbirefringent and are known as the I (isotropic) bands. The I-bands are bisected by a dense line, known as the Z-line or Z-membrane. The

Z-membranes appear to be continuous across the whole width of the fiber and to hold the fibrils in register; there is evidence[4] that they may provide the path along which the signal for contraction is transmitted into the interior of the fiber.

This pattern has been described in some detail, for its features are not of merely morphological interest: they are the visible expression of the highly organized molecular structure responsible for contraction; they are related to that structure in a remarkably simple way; and once that relationship has been recognized they can give very specific information about the nature of the molecular changes taking place during contraction.

STRUCTURE VISIBLE IN THE ELECTRON MICROSCOPE

When muscle is examined in the electron microscope, it is found that the myofibrils themselves are built up of smaller longitudinal filaments having diameters of the order of 100 Å. These filaments remain straight when the muscle contracts. They form a continuous array across the whole width of the myofibrils, being spaced out a few hundred Ångström units apart; in life, the space between them is filled with a solution of salts and soluble proteins. The array of filaments is quite crystalline in its regularity, and living muscle will reflect x-rays quite strongly at the appropriate angles.[5]

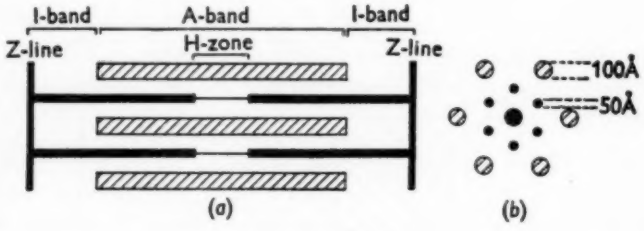
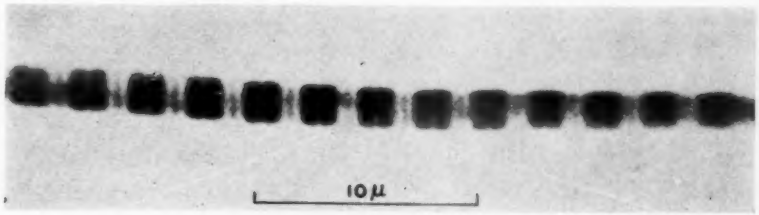
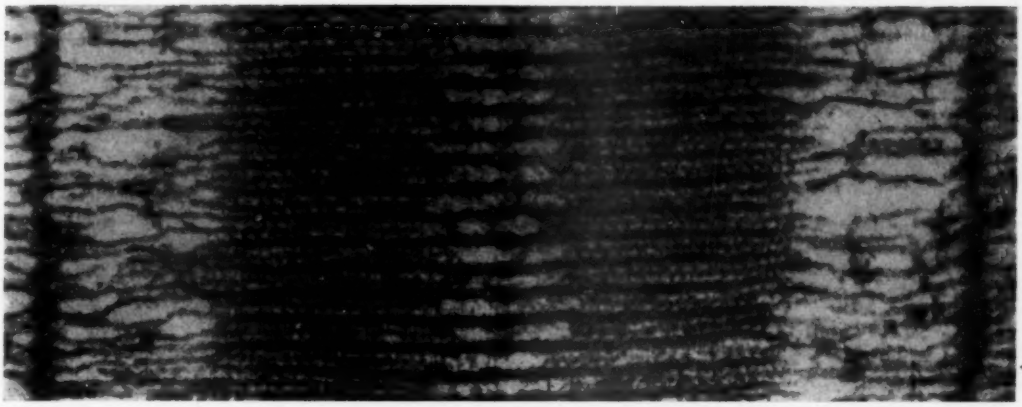


Fig. 2.—Diagrammatic representation of arrangement of filaments in striated muscle: (*a*) longitudinal; (*b*) sectional.

Within the last few years, technical developments have made it possible to cut sections of muscle and other biological tissues which are sufficiently thin to be examined in the electron microscope. This has greatly extended the range of usefulness of the instrument, and, because of the extreme thinness of the sections (only 100 or 200 Ångström units), has made it possible to achieve resolution of the order of 30 Å on biological material. Examination of electron micrographs of very thin cross sections of muscle reveals some remarkable features about the structure.[6] Cross sections through the denser parts of the A-band (i.e., the regions on either side of the H-zone) show that two different types of filaments are present here (Fig. 4, *A*). First, there is a hexagonal array of "primary" filaments about 100 Å in diameter and spaced about 200 to 300 Å apart. The spacing as measured by x-ray diffraction in living muscle is 450 Å, and the lower value seen here is probably due to shrinkage during the preparation of the material for sectioning. Between the primary filaments a secondary array of thinner filaments, about 40 to 50 Å in diameter, can be seen; each secondary filament lies symmetrically between three



A.



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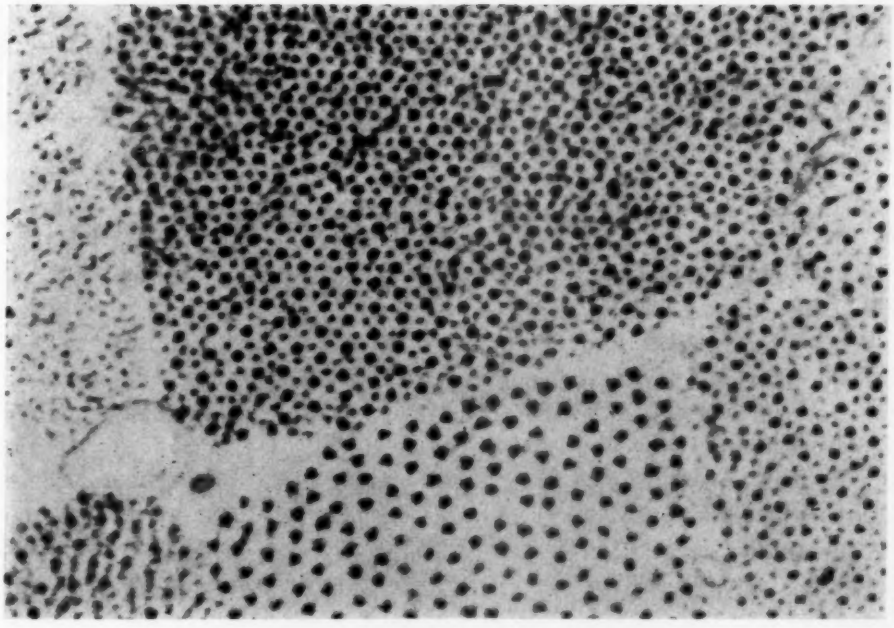

C.

Fig. 3.—*A*, Myofibril from rabbit psoas muscle, photographed in phase-contrast illumination. Note dense A-bands; the I-bands are less dense and are bisected by the Z-lines. *B*, Same as in *A*, as seen in electron microscope (longitudinal section). *C*, Cross section of muscle, showing the continuous array of filaments; in the center of the picture the section has passed through an H-zone and a simple array is visible; on either side the compound array present in the rest of the A-band may be seen. (Magnification, × 115,000.)

primary filaments, so that each primary filament has around it six secondary filaments which it shares with its six nearest neighbor primary filaments. The arrangement is shown diagrammatically in Fig. 2.

Sections through the central region of the A-band, the H-zone, show only the hexagonal array of primary filaments (see Fig. 4, *B*), and any secondary filaments in this region must be so thin as to escape detection. Sections through the I-band show only thin filaments of diameter about 50 Å, and the hexagonal array of primary filaments is not present in this band, as indeed is obvious from longitudinal sections (see Fig. 3,*B*).

The conclusion from these observations is a very straightforward one. It is simply that the fibrils are built up of two overlapping, interpenetrating arrays of longitudinal filaments (Fig. 2). The thick filaments are confined to the A-band and produce the high density and birefringence of that band. Thin filaments extend in either direction from the Z-line, through the I-band, into the A-band, and terminate or become much thinner at the edge of the H-zone. The densest zone of the band pattern occurs where the two arrays of filaments overlap, i.e., in the region of the A-band on either side of the H-zone. The next densest zone occurs where the thicker filaments are present on their own, i.e., in the H-zone. The least dense band occurs where thin filaments alone are present, i.e., in the I-band, for although there are twice as many of them as there are thick filaments, the cross-sectional area of each one of them is only about one quarter as great. This concept of the structure has been confirmed by recent electron-microscope studies on ultra-thin longitudinal sections of striated muscle[31] in which the two types of filament can be seen clearly lying side by side in the A-bands (see Fig. 11).

We see then that the visible striated appearance of skeletal muscle arises directly from the organization of the contractile material of the myofibrils into two distinct, overlapping arrays of filaments.

BAND PATTERN CHANGES DURING CONTRACTION AND STRETCH

The A- and I-bands have lengths of the order of 1 micron. Thus in the physiological range of contraction the changes in band length can be only fractions of a micron. Such small changes are difficult to measure, particularly when they are taking place very rapidly, and the measurements are very susceptible to optical artifact. Fixing the muscle prior to examination in the light microscope or the electron microscope does not really solve the problem, for the fixation process may itself introduce changes in band length. It is only in the last few years, with the introduction of the phase-contrast and interference microscopes, that accurate and dependable measurements have become technically possible.[7,8] The results are remarkably simple. Consider, for example, skeletal muscle from the rabbit or the frog. At resting length, the distance between successive Z-lines, which defines the repeating period of the cross-striations, is 2.3 microns; the length of the A-band is 1.5 microns and that of the I-band 0.8 micron. When the muscle contracts, the A-band remains at constant length and the I-band decreases in length until it disappears altogether at about 65 per cent of the resting length. This is the normal limit of physiological contraction, and further shortening

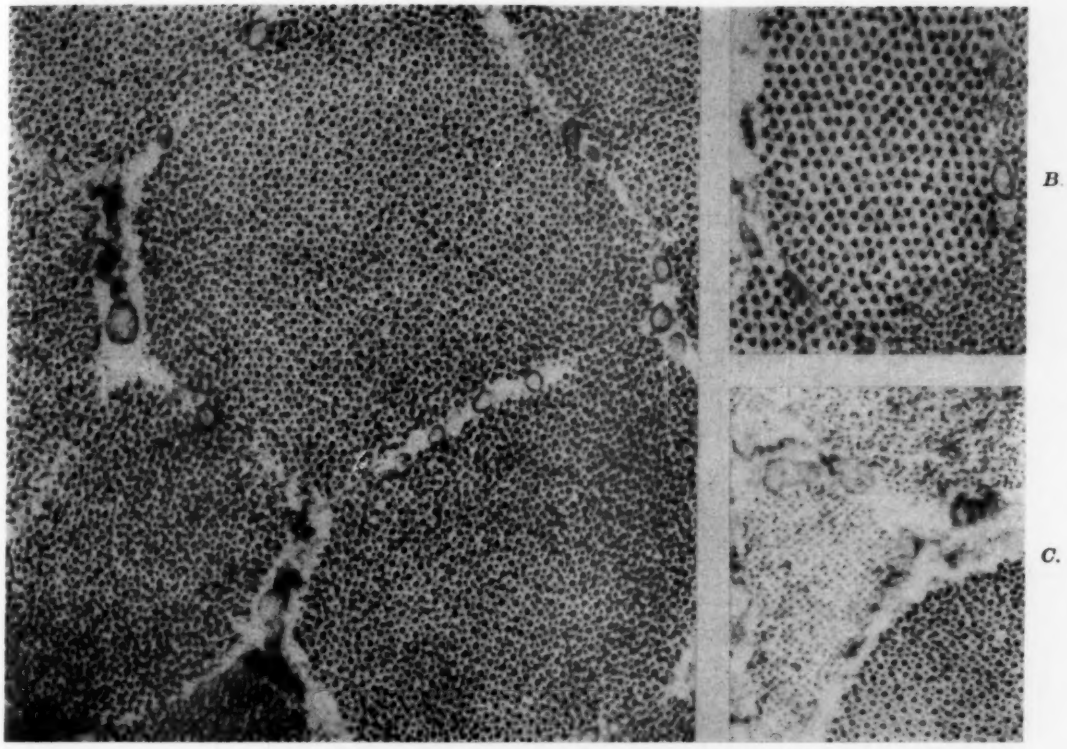

Fig. 4.—Electron micrographs of cross section of rabbit psoas muscle (stained with osmic and phosphotungstic acids). *A*, Section showing double hexagonal array of filaments in A-bands. *B*, Section showing simple hexagonal array of thick filaments in H-zone. *C*, Section showing (left-hand side and top) array of thin filaments in I-band. Note double array in neighboring fibril sectioned in A-band. (Magnification, × 45,600.)

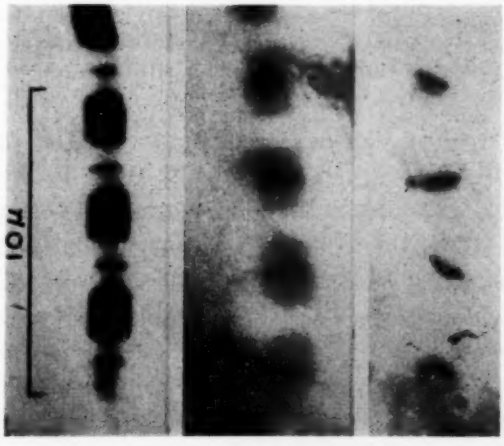

Fig. 5.—Extraction of proteins from myofibril: *A*, before extraction; *B*, after extraction of myosin (note removal of A-substance); *C*, after extraction of actin; only Z-lines and some backbone material remain.

beyond this point produces dense contraction bands where adjacent A-bands have been brought into contact at the Z-line. In Figs. 6 and 9 these changes are illustrated both diagrammatically and as they take place in a single muscle fibril observed in the phase-contrast microscope.

If relaxed muscle is stretched, the A-bands remain at constant length and the increase in length is taken up by the I-bands. During contraction from a stretched condition the same process happens in reverse. During an isometric contraction, when the muscle exerts a force but is not allowed to shorten, neither the A- nor the I-bands change in length. It appears that under all conditions the band pattern is determined simply by the length of the muscle, and is the same whether the muscle is in the active state or not. Moreover, the same band pattern changes are observed in experiments both on living fibers contracting under normal physiological conditions and on isolated fibrils made to contract by biochemical means.

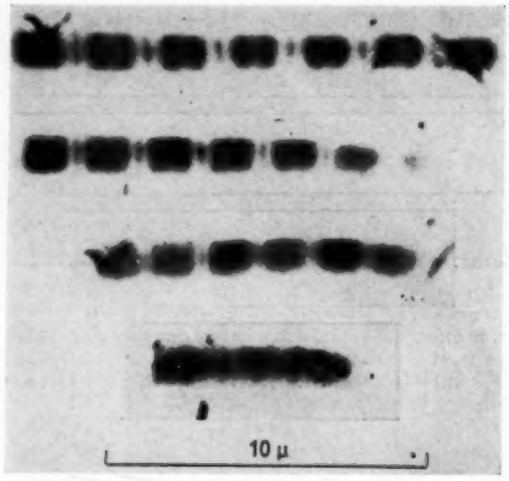

Fig. 6.—Myofibril from rabbit psoas muscle, photographed in phase-contrast illumination at successive stages of an ATP-induced contraction. Note shortening of I-bands and disappearance of H-zones.

One further, and most illuminating, feature of the band-pattern changes should now be described. It will be recalled that the central region of the A-band, the H-zone, is somewhat less dense than the regions on either side of it. When the muscle increases in length, the H-zone increases in length by the same amount, although the total length of the A-band remains constant. Thus the distance from the Z-line to the edge of the H-zone remains constant (see Fig. 8). The appearance of a stretched fibril, with its very long H-zone, is shown in the electron micrograph reproduced in Fig. 7. During shortening, the H-zone decreases in length until it disappears at about 85 per cent of the resting length; it is replaced by a dark line if further shortening occurs.

These observations have a very simple explanation, which becomes particularly obvious when the electron microscope observations are kept in mind. It is that the two arrays of filaments, whose lengths define the length of the A-band and the distance from the Z-line to the edge of the H-zone, always remain, so far

as possible, at constant length, and that changes in the length of the muscle are brought about simply by the two arrays sliding into or out of each other.[7,8] If the muscle contracts too far, the filaments of one or of both arrays will have to crumple up at the ends for steric reasons, but over a considerable range of lengths the sliding process alone takes place. Additional support for this hypothesis is provided by the x-ray diffraction data.

Fig. 7.—Electron micrograph of longitudinal section of stretched muscle; note long H-zones.

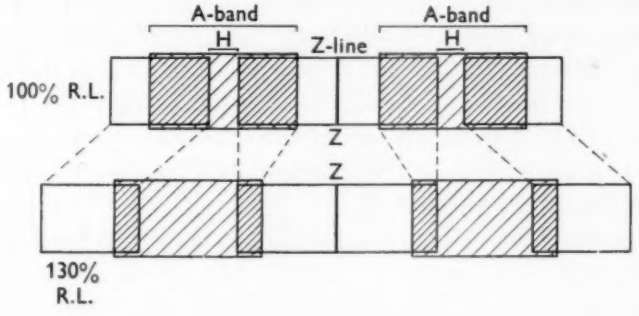

Fig. 8.—Diagram of band-pattern changes during muscle stretch; the distance from the Z-line to the edge of the H-zone remains constant. *R.L.* = Resting length.

X-RAY DIFFRACTION EVIDENCE

The filaments seen in electron micrographs of muscle often show a longitudinal periodicity of about 400 Å, and a similar axial period (415 Å) has been demonstrated in low-angle x-ray diffraction diagrams obtained from living muscle.[5] The x-ray reflections are very sharp and show that the periodicity must be maintained with almost atomic precision. When a living muscle is stretched, the x-ray period does not increase, and diagrams obtained from artifically contracted muscle suggest that the period remains constant there too. It is not clear at present whether the x-ray period arises from the internal structure of only one type of filament or of both types. However, whichever is the case, the x-ray evidence shows that the structure which gives rise to the 415 Å axial period does not change in length when the muscle changes in length. This result is in perfect accord with a sliding-filament model.

No characteristic changes associated with contractions have been observed in the wide-angle x-ray diagram given by muscle.[9] This again shows that the major part of the internal structure of the filaments retains a constant atomic configuration during contraction.

From the light microscope and electron microscope evidence, and from the x-ray data, the conclusion seems inescapable that contraction is brought about by some mechanism which causes the two different types of filament to slide past each other. We must now inquire what is the composition of these filaments, and what interactions between them might cause such a sliding process to occur.

THE PROTEIN COMPONENTS OF MUSCLE

Muscles contain about 20 per cent of protein and 80 per cent of dilute salt solution. About two thirds of the protein is present in fibrous form and constitutes the contractile structure of the muscle. Other proteins present include enzymes for facilitating reactions which convert the energy-rich compound glycogen from the blood stream into another compound which can be used directly as an energy source by the contractile machinery. These metabolic reactions synthesize adenosine triphosphate (ATP), and it has long been realized that the hydrolysis of this compound to adenosine diphosphate (ADP) was a reaction very closely linked to the contractile process. Although this reaction can be demonstrated as taking place in contractions of appreciable duration, attempts to demonstrate any breakdown of ATP during a single twitch have not been successful.[10,11] It remains in doubt, therefore, whether some other compound, itself synthesized from ATP, might not be the immediate source of energy, or even whether the contractile mechanism might not itself be able to perform one twitch without an external supply of energy.

The two great simplifying discoveries in muscle biochemistry which have enabled thought and experiment to be directed at the real essentials of the problem of contractility are concerned with the structural proteins. Two of these, actin and myosin, are of special importance and together make up about half the total protein in muscle. Myosin had for a very long time been recognized as a typical fibrous protein, and it was generally believed that some change in the configuration of the myosin molecule was the factor responsible for muscular contraction. It was a considerable sensation, therefore, when the discovery was made[12] that myosin is itself the enzyme which catalyzes the breakdown of ATP to ADP.

Perhaps even more dramatic still was the discovery that artificial fibers made from a mixture of actin and myosin extracted from muscle will contract when they are placed in a suitable solution containing ATP.[13,14] These discoveries showed that the entire basic mechanism of contractility is contained in the actin-myosin-ATP system.

PROPERTIES OF MYOSIN AND ACTIN

Myosin has a molecular weight often reported to be 800,000 (see, for example, Reference 15), but is now reported as being only half that value.[16] The molecule

is long and thin, and light-scattering and other measurements[15,17] give a length in the range of 1,500 to 2,000 Å, with a diameter of about 20 Å. Actin has a molecular weight of about 70,000,[15] but its shape is uncertain. It can exist in solution in two different forms. One form is known as globular or G-actin, and seems to consist of either single molecules or dimers. When salt is added to solutions of G-actin, another form, known as fibrous or F-actin, is produced. One might therefore expect the actin in muscle to be present as F-actin. Solutions of F-actin

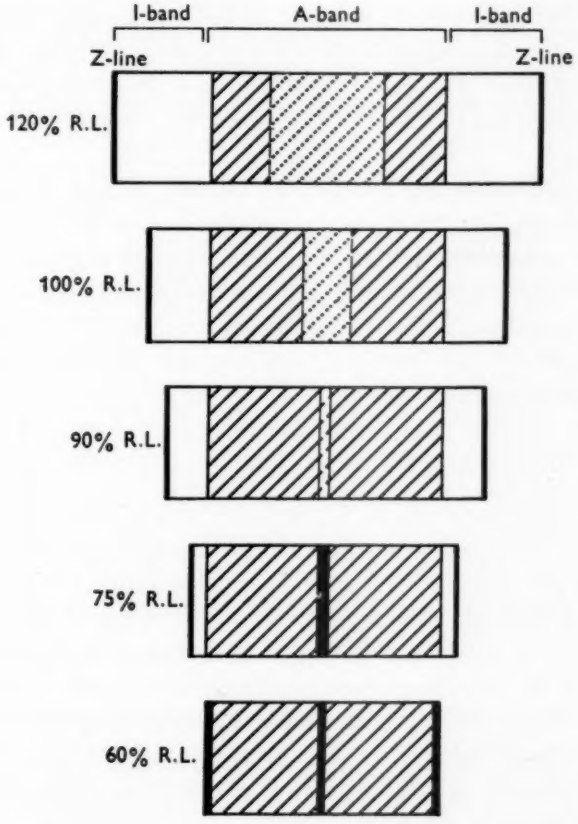

Fig. 9.—Diagrammatic representation of band-pattern changes during contraction.

have a high and anomalous viscosity, exhibit strong flow-birefringence, develop birefringence spontaneously on standing, and display many other characteristics to be expected of long polymers of G-actin units. They have two very interesting features. If actin is labeled with a fluorescent dye, then the rotational periods of the G-actin units in F-actin can be calculated from measurements of the depolarization of fluorescent radiation. These measurements lead to the conclusion that the G-actin units in fibrous actin have freedom of rotation about at least one axis.[18] It is also found that globular actin has ATP bound to it, and that the ATP is transformed into ADP when G-actin polymerizes to form F-actin.[19]

When solutions of actin and myosin are mixed together, the viscosity of the mixture is considerably higher than the sum of the viscosities of the constituents.

If the mixture is centrifuged at high speed, almost all the protein forms a compact pellet of sediment, whereas under similar conditions myosin on its own would remain largely in the supernatant.[20] It is clear that some sort of complex can form between actin and myosin; this is known as actomyosin. If ATP is added to a solution of actomyosin in 0.6M KCl, a large fall in viscosity occurs, and myosin, and only myosin, can be recovered from the supernatant left after a degree of centrifuging that would bring down actomyosin and F-actin.[20] It seems, then, that at this salt concentration, ATP dissociates the actomyosin complex into actin and myosin; ATP is itself split by myosin, and when all the ATP has been hydrolyzed in this way, the actomyosin complex re-forms. At lower salt concentration (e.g., 0.1M) ATP brings about the precipitation of actomyosin from solution. And when the actomyosin has been orientated into threads, ATP produces contraction.

If the actin molecules are labeled, as before, with a fluorescent dye, they will still form actomyosin; fluorescence depolarization measurements show that the actin units in actomyosin behave as monomers having freedom of rotation about at least one axis; when actomyosin is dissociated by ATP, the actin immediately behaves as though it were composed of dimers.[21] These are all fascinating and rather baffling relationships, and no comprehensive scheme that will explain all of them has yet been evolved.

MODEL SYSTEMS

The inter-reaction between actin, myosin, and ATP can also be studied very profitably in model systems which lie in their complexity part way between the purified protein solution and the living fiber. The first of these, the actomyosin thread, has already been mentioned. The second is the so-called glycerol-extracted fiber model. It was found by Szent-Györgyi[22] that muscle fibers which had been kept cold in 50 per cent glycerol for a few days or weeks would, though of course no longer electrically excitable, contract when placed in suitable solutions containing ATP. It has been found that this contraction imitates in very many respects the contraction of a living fiber, although it takes place more slowly. The maximum tension exerted is roughly the same.

The glycerinated fibers are normally inextensible and resemble muscle in rigor, for they have lost the ATP which fresh, living muscles contain. If, after an ATP-induced contraction, the ATP is washed out of such a fiber model, then the fiber "sets" at the shortened length. If, however, the dephosphorylation of ATP is inhibited either by an enzyme poison, for instance Salyrgan, or by a factor[23] which can be extracted from fresh muscle, then not only is contraction abolished, but the fiber may now be readily re-extended to its original length. Under these conditions ATP is said to act as a plasticizer.

Certain inorganic phosphates, as for instance sodium pyrophosphate,[24] also produce a plasticizing effect on glycerinated muscle; these compounds are not dephosphorylated by myosin, but they all have the property of lowering the viscosity of an actomyosin solution; so, like ATP, they can presumably dissociate the actomyosin complex.

These observations may be compared with the behavior of living muscle fibers. These contain ATP, but in the resting state the enzymatic activity of myosin is inhibited in some way and ATP breakdown is very slow; the fibers are quite flexible and may be stretched easily. During contraction the muscle becomes quite rigid, but regains its plasticity when the contraction is over. If the muscle is allowed to pass into rigor, a condition associated with the loss of ATP, then the fibers will no longer contract, and they become rigid and inextensible.

It seems, then, that ATP performs a dual role in muscle. When dephosphorylation cannot take place, the presence of ATP keeps the muscle plastic and extensible; when dephosphorylation can take place, the presence of ATP causes contraction.

BIOCHEMICAL CONCLUSIONS

We may summarized the biochemical evidence as follows: (1) The contractile structure is built largely out of two proteins, actin and myosin. (2) Some sort of combination can occur between actin and myosin. (3) This combination is modified by the presence of ATP. (4) Myosin is an enzyme for the dephosphorylation of ATP. (5) The dephosphorylation of ATP is very closely linked with the release of energy for contraction. (6) The presence of ATP without dephosphorylation makes the contractile structure extensible. (7) Other substances which, like ATP, dissociate actomyosin, also make the contractile structure extensible. (8) In the absence of ATP or other plasticizer the contractile structure becomes rigid and inextensible.

Let us now see what expression these concepts find in our structural knowledge of muscle.

THE PROTEIN COMPOSITION OF THE FILAMENTS

Myosin can be dissolved out from either whole muscle or from isolated myofibrils by procedures which remove little or no actin.[25] Microscopic observations[26,27] show that the removal of myosin is associated with the extraction of the dense material of the A-bands, i.e., of the so-called A-substance. This is illustrated in Fig. 5, which shows an isolated myofibril before and after myosin has been extracted from it. A "ghost" fibril is left, consisting of material extending from the Z-lines to the edge of what was formerly the H-zone; the H-zones now have a very low density, but the fibril structure is still continuous across them. The ghost fibrils will not contract in solutions containing ATP. In the electron microscope it can be seen that the array of thick filaments which characterized the A-bands of normal muscle is no longer present. Moreover, quantitative measurements made with the interference microscope[28] show that the amount of A-substance, present in intact fibrils and removed from them when myosin is extracted, is exactly equal to the myosin content of the fibrils given by biochemical analysis. One can conclude, therefore, that the thick filaments seen in the electron microscope in the A-bands of muscle are made up very largely of myosin.

After myosin has been removed from muscle, actin can be extracted by another procedure. When the ghost fibrils remaining after myosin extraction are treated in the same way, then most of the residual material between the Z-line and the edge of the H-zone is removed (see Fig. 5). It will be remembered from the account of electron-microscope observations that this material consists of the thin filaments which formed the secondary hexagonal array where they overlapped with the thick filaments in the A-band. Thus, one must conclude that these secondary filaments contain the protein actin.

One arrives, therefore, at the very simple concept that the two principal contractile proteins of muscle, actin and myosin, are organized into separate filaments; and that the interaction of actin and myosin filaments with ATP causes them to slide past each other (Fig. 10). It is in the light of this model that a relation should be sought between the biochemical observations and the physiological behavior of muscle.

CORRELATION OF STRUCTURE, BIOCHEMISTRY, AND PHYSIOLOGY

The construction of striated muscle in this particular fashion would appear to offer two advantages from the mechanical point of view. These arise from the two basic features of the structure—the discontinuous nature of both the actin and the myosin filaments, and the fact that groups of filaments of any one type are arranged in register. In the first place, a considerable amount of shortening can take place without either type of filament having to fold up in any way. Secondly, the filaments within any given array do not move relative to each other, and so internal frictional losses will be kept at a minimum. The arrangement looks neat, efficient, and well adapted to carrying out rapid contractions.[29]

A good starting point to show the way in which the different types of information about muscle are beginning to fit together is provided by the behavior of muscle when it is stretched. During stretch we have seen that the actin filaments are drawn further out of the array of myosin filaments. If cross-links were to be formed between the actin and the myosin filaments, then, if the filaments themselves were inextensible, the muscle too would be inextensible. Such cross-links would correspond to the combination that can take place between actin and myosin in solution. ATP is believed to dissociate this combination, and one might therefore expect it to break the cross-links between actin and myosin filaments. Thus, the observation that muscle and muscle models are extensible only in the presence of ATP, or of other substances which can dissociate the actomyosin complex, can be accounted for in an extremely simple way.

CONTRACTION MECHANISMS

The picture of contraction which has now emerged may be summarized as follows. In the resting state, the two overlapping arrays of filaments are not linked to each other because of the presence of ATP and the absence of ATP breakdown. When the muscle is stimulated, the release of some activator allows the enzymatic breakdown of ATP to commence. An interaction between myosin, actin, and ATP takes place and, as a result, the array of actin filaments is drawn further into the

array of myosin filaments, producing shortening of the muscle and the observed change in band pattern. When ATP breakdown ceases, its interaction with myosin and actin no longer produces contraction but simply breaks the links between the two filaments; the muscle can then be re-extended. In the case of a glycerinated fiber the process is similar, except that ATP breakdown, and contraction, begin as soon as ATP is supplied to the fiber, and finish only when ATP is washed out of the fiber, leaving it locked at its shortened length. The essential feature is that actin filaments are made to slide past myosin filaments by a reaction in which the dephosphorylation of ATP is involved but the details of which remain unknown. This feature sheds new light on a number of aspects of muscular contraction, which we will now consider briefly.

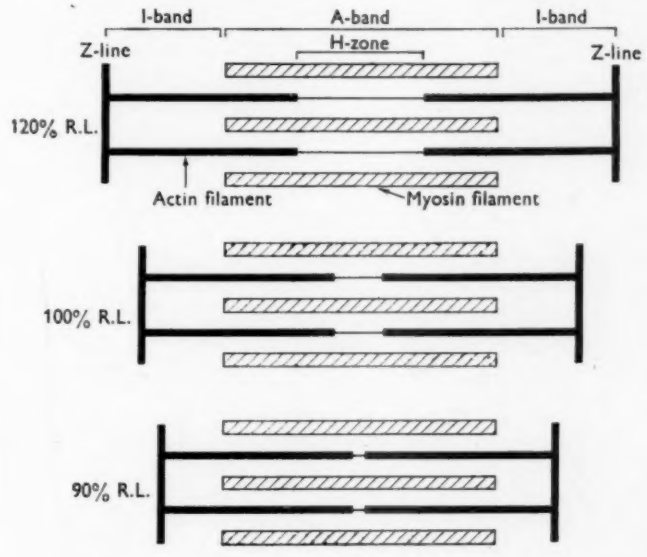

Fig. 10.—Diagram showing behavior of actin and myosin filaments during changes of muscle length.

Each filament contains several hundred actin or myosin molecules. The x-ray diffraction evidence shows that in at least one type of filament, and perhaps in both, the molecules form a regularly repeating pattern. In the region where the two arrays of filaments overlap, myosin-actin interactions are likely to take place at a large number of points where actin and myosin molecules come into apposition. These interactions cause the two filaments to slide past each other. Each time the filaments move relative to each other by a distance equal to their axial periodicity, then virtually the same spatial pattern of interactions between them will recur. One might therefore expect the system to work in a step-by-step fashion, each complete contraction of the muscle being brought about by the repetition of a number of identical contractile events at the sites of myosin-actin interaction.

A possible mechanism could consist of obliquely oriented cross-linkages extending from the myosin molecules on one filament to the actin molecules on the other; the cross-linkages could form part of the myosin molecule itself.

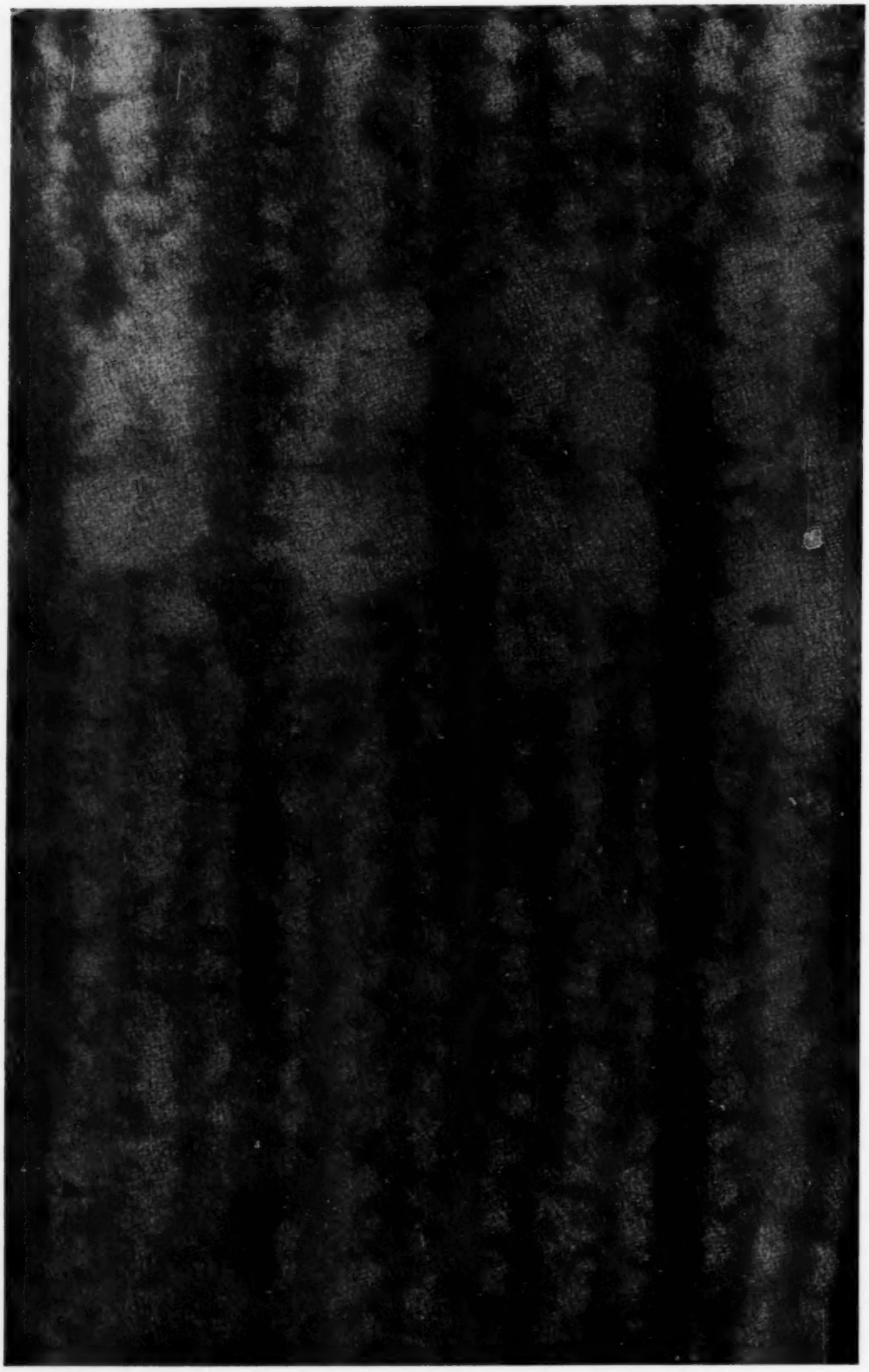

Fig. 11.—Highly magnified view of ultra-thin section through A-band (including H-zone) of rabbit psoas muscle. Thick and thin filaments may be seen lying side by side, linked together by a system of cross-bridges. The thin filaments terminate at the boundaries of the H-zone. The fact that pairs of thin filaments are seen between the thick ones is a consequence of the geometry of the double hexagonal array and the direction of the plane of sectioning. (Magnification, × 540,000.) (From Huxley: Journal of Biophysical and Biochemical Cytology, Volume 3, 1957, page 631.)

Shortening of the link would pull the actin filament along a short distance. The link could then be detached from the actin molecule (say by the arrival of a molecule of ATP), re-extend again, attach to the actin filament a little further along, and the whole process be repeated. A more complicated mechanism involving repetitive alternations in length of the actin filaments has also been discussed.

Whatever the details of the mechanism, however, the same basic property remains: a number of minor cycles of a detailed molecular process take place within the major cycle of contraction and relaxation of the muscle itself. Thus, one cannot simply equate the return of the muscle to its resting length with the re-extension of the contractile material; hence, arguments about whether muscle as a whole relaxes actively or passively, although very important in many other respects, have no direct relevance to the question whether the contractile material extends actively or passively at the molecular level. Another feature of this type of mechanism is that each enzyme site—that is, each myosin molecule—can take part in the reaction a large number of times during each over-all contraction cycle. The total work done per cycle will therefore be much greater than in a system in which each link can shorten only once per cycle, as for instance would be the case if the shortening of a number of links were added up in series.

A system of links, acting in parallel and having to break and re-form each time a small amount of shortening takes place, has another interesting property. If a finite time is required for each link to form, then the number of links in existence at any particular moment, and hence the total tension exerted, will be a function of the speed of shortening. If the system is prevented from shortening, then there will be time for the maximum possible number of links to form, and the tension will be a maximum. Making a small number of assumptions, it can be shown that in such a system the rate of energy release varies with load in a manner which imitates closely the simple and striking behavior of muscle itself.[30]

The observations lead, then, to a mechanism whose general behavior fits in very well with the physiological properties of muscle. The basic nature of this mechanism, however, still remains unknown. We still require electron micrographs which show the internal structure of the filaments and the details of any cross-connections between them; the details of the x-ray diffraction diagrams remain uninterpreted; and the actin-myosin-ATP interaction has still to be described in detailed terms. There is every hope that, along these lines, the problem of muscular contraction can be solved.

I am much indebted to my colleague Dr. Jean Hanson; many of the ideas discussed in this article were the outcome of our collaboration, and the light-microscope photographs shown are taken from our joint publications. Many similar ideas have been developed by A. F. Huxley and R. Niedergerke.

REFERENCES

1. Hill, A. V.: Proc. Roy. Soc., London, ser. B **126**:136, 1938.
2. Hill, A. V.: Proc. Roy. Soc., London, ser. B **136**:195, 1949.
3. Hill, A. V.: Proc. Roy. Soc., London, ser. B **136**:399, 1949.
4. Huxley, A. F., and Taylor, R. E.: J. Physiol. **130**:49, 1955.
5. Huxley, H. E.: Proc. Roy. Soc., London, ser. B **141**:59, 1953.
6. Huxley, H. E.: Biochim. et biophys. acta **12**:387, 1953.

7. Huxley, A. F., and Niedergerke, R.: Nature, London **173**:971, 1954.
8. Huxley, H. E., and Hanson, J.: Nature, London **173**:973, 1954.
9. Astbury, W. T.: Proc. Roy. Soc., London, ser. B **134**:303, 1947.
10. Fleckenstein, A., Janke, J., Davies, R. E., and Krebs, H. A.: Nature, London **174**:1081, 1954.
11. Mommaerts, W. F. H. M.: Nature, London **174**:1083, 1954.
12. Engelhardt, W. A., and Ljubimowa, M. N.: Nature, London **144**:669, 1939.
13. Szent-Györgyi, A.: Stud. Inst. med. Chem. Univ. Szeged **1**:17, 1942.
14. Weber, A., and Weber, H. H.: Ztschr. Naturforsch. **5b**:124, 1950.
15. Weber, H. H.: Proc. Roy. Soc., London, ser. B **137**:50, 1950.
16. Laki, K., and Carroll, W. R.: Nature, London **175**:389, 1955.
17. Mommaerts, W. F. H. M.: J. Biol. Chem. **188**:553, 1951.
18. Tsao, T.-C.: Biochim. et biophys. acta **11**:227, 1953.
19. Straub, F. B., and Feuer, G.: Biochim. et biophys. acta **4**:455, 1950.
20. Weber, A.: Biochim. et biophys. acta **19**:345, 1956.
21. Tsao, T.-C.: Biochim. et biophys. acta **11**:236, 1953.
22. Szent-Györgyi, A.: Chemistry of Muscular Contraction, ed. 2, New York, 1951, Academic Press.
23. Marsh, B. B.: Biochim. et biophys. acta **9**:247, 1952.
24. Weber, H. H., and Portzehl, H.: Progr. Biophys. **4**:60, 1954.
25. Hasselbach, W., and Schneider, G.: Biochem. Ztschr. **321**:461, 1951.
26. Hanson, J., and Huxley, H. E.: Nature, London **172**:530, 1953.
27. Hasselbach, W.: Ztschr. Naturforsch. **8b**:449, 1953.
28. Huxley, H. E., and Hanson, J.: Biochim. et biophys. acta **23**:229, 1957.
29. Hanson, J., and Huxley, H. E.: Symp. Soc. Exper. Biol. **9**:228, 1955.
30. Huxley, A. F.: Progr. Biophys. **7**:257, 1957.
31. Huxley, H. E.: J. Biophys. & Biochem. Cytol. **3**:631, 1957.

Annotations

Amine Oxidase Inhibitors and Angina Pectoris

Within the past three years considerable evidence has accumulated demonstrating the relief of pain in patients with angina pectoris treated with the amine oxidase inhibitors. At least 12 articles in the literature point out the effectiveness of iproniazid (Marsilid) In this regard. Recently, Kennamer and Prinzmetal have pointed out the value of B-phenylisopropylhydrazine hydrochloride (Catron, also designated JB 516, Lakeside Laboratories). In addition to Marsilid and Catron other drugs capable of inhibiting the action of monoamine oxidase are under study. These drugs include B-phenethyl-hydrazine hydrogen sulfate (Nardil, Warner-Lambert Laboratories), 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine (RO 5-0831/1, Hoffmann-La Roche Laboratories) and N-isonicotinoyl-N′-(B-N-benzylcarboxamido-ethyl)-hydrazine (Niamid, Pfizer Laboratories). All of these drugs apparently have in common the ability to inhibit the pain of angina pectoris.

The mechanism of pain relief has not been established. It has been suggested that these compounds have a sparing action on serotonin, norepinephrine, epinephrine, and their precursors, and it has been shown that the intracoronary arterial injection of these agents (serotonin, norepinephrine and epinephrine) produces an increase in coronary blood flow after the MAO inhibitors. It seems unlikely that relief of pain is the result of the elevation in mood which some depressed patients experience, for it commonly happens that chest pain is relieved when the mood is unchanged. An intriguing thought is the possibility that ganglionic blockade (possibly sympathetic) interferes with the transmission of pain impulses from the heart to the brain. Gertner[1] has recently demonstrated that at least three of the MAO inhibitors are capable of blocking the superior cervical ganglion of the cat. He theorizes that inhibition of MAO allows a substance to accumulate at or in ganglia which inhibits impulse transmission. The effect of the MAO inhibitors on other amines is being explored and it has already been shown that the cardiovascular actions of tyramine, dopamine, and tryptamine are markedly potentiated after the administration of the inhibitors.

The greatest hazard associated with the use of these agents in the cardiac patient is postural hypotension, especially among patients receiving chlorothiazide or hydrochlorothiazide concomitantly, patients with postcoronary angina pectoris whose blood pressure tends to be low, and certain normotensive individuals with a tendency to postural hypotension. The value of pain relief in angina pectoris should be weighed carefully against the risk of myocardial ischemia or myocardial infarction related to postural hypotension. The MAO inhibitors should be used with great care when the coronary artery disease is advanced, as slight postural hypotension could result in serious myocardial ischemia, infarction, or a fatal cardiac arrhythmia. Although it has been shown that the monoamine oxidase inhibitors effectively relieve pain in a significant percentage of patients, basic improvement in the disease state, for example the return of abnormal electrocardiograms to normal ones, has not as yet been established.

Other side effects are seen; however, they are infrequent and are less hazardous than postural hypotension to the cardiac patient. Hepatitis apparently is relatively rare in patients receiving Marsilid (approximately 1 per 4,000 patients); however, when it occurs, more than 22 per cent of the patients afflicted succumb. It is too early to determine the hepatotoxicity of the newer MAO inhibitors at this time.

It appears that less toxic agents should be employed initially for the relief of pain in angina pectoris and that the MAO inhibitors may be used when simpler and safer methods are ineffective.

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REFERENCE

1. Gertner, Sheldon B.: Ganglionic Block and Monoamine Oxidase Inhibitors, Nature, 183:750, March 14, 1959.

Digitalis

The pendulum in research sometimes swings slowly and often internationally. This is particularly true with reference to digitalis. It is surprising how much difference of opinion still is found among clinicians on the use of this drug, despite the enormous literature available, and also how much prejudice exists even among investigators.

Withering originally used digitalis for dropsy, being unaware of the existence of auricular fibrillation which was described later, chiefly by Mackenzie. It was Mackenzie and Lewis who emphasized the use of the drug for auricular fibrillation with congestive heart failure, using ventricular rate as an index of its effectiveness. Later, in the United States and in Austria, the drug was advocated for all cases of congestive failure, regardless of associated arrhythmias, the chief protagonists of this point of view being Christian and Wenckebach.

The latter point of view received support from physiologists such as Cournand working with the cardiac catheter, although it remained difficult in the intact animal to be sure whether the effect of the drug was direct on the heart or at least in part indirect via peripheral blood vessels. There was some conflict of opinion, for example, as to whether the drug was effective in the isolated heart.

From a more practical standpoint, however, considering the effectiveness and availability of modern diuretics, does digitalis add anything to the management of congestive heart failure with sinus rhythm? Some workers insist that it does and others that it adds nothing, or at most very little. They also point to the ease with which digitalis toxicity is produced in such cases.

The whole question is complicated by the fact that congestive failure is not a steady state but is exacerbated by such events as pulmonary embolism, infection, dietary indiscretion, etc. The question of whether or when to use digitalis in the presence of arrhythmias, with or without congestive failure, is even more complex. All this confusion, however, has one salutary effect. It becomes clear that digitalis must not be given as a "routine" drug for heart disease regardless of whether there is an arrhythmia, congestive heart failure, or both. When the drug is given or withheld, the decision must always be preceded by a careful evaluation of all factors and objectives in each individual case.

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Physiologic Abnormalities and Clinical Diagnosis

When measurements of physiologic parameters are applied to clinical diagnosis, utility combines with scientific reason. When such application promises aid in diagnosis of a common clinical problem, the method deserves detailed consideration.

Such a situation is encountered in the recent report by Robin, Julian, Travis, and Crump[1] on the diagnosis of acute pulmonary embolism from measurements of end-tidal and arterial PCO_2. The method is based on the observation that ordinarily there is close agreement between arterial and alveolar PCO_2 (no a-A gradient) but that following acute pulmonary embolism the alveolar gas will be diluted by contributions from ventilated but poorly perfused segments of the

lung and this will cause a significant a-A PCO_2 gradient. In other words, the demonstration of an arterial-alveolar PCO_2 gradient in a given nonemphysematous subject suggests the diagnosis of acute pulmonary embolism.

It seems to us that this statement must rest on two assumptions and implies a third, as follows: (1) There is no PCO_2 gradient unless some form of cardiopulmonary disease is present. (2) Clinical entities which might become confused with pulmonary vascular obstruction (pneumonia, bronchial obstruction) will not cause physiologic alterations similar to those observed in pulmonary artery embolism. (3) The physiologic mechanism claimed as the cause for the abnormal measurement is exclusively or predominantly responsible for the observed phenomenon.

In general, the first assumption is valid in normal subjects in a supine position. Yet, Martin[2] has shown recently that erect posture causes alterations in the ventilation-perfusion relationships due to relative hyperventilation and underperfusion of the upper lobes resulting in a-A PCO_2 gradients in excess of 9 mm. Hg. Rapid ventilatory rates also may be the cause for such a gradient. If, for some reason (anxiety, dyspnea), the measurements were made in the semierect position or if tachypnea was present or both, a significant PCO_2 gradient might have occurred on this basis alone. In consequence, present evidence does not support the assumption that a significant a-A PCO_2 gradient may not be found in the absence of disease.

The second assumption is based on the observation that any disturbance in ventilation-perfusion ratios in the lung will result in a PCO_2 gradient, but that ventilation without perfusion will exert a greater effect than that of an equivalent fraction of lung which is perfused but not ventilated.[3] This conclusion depends upon the presence of a small mixed venous to pulmonary capillary PCO_2 difference (about 10 mm. Hg) under normal circumstances. It is reasonable to expect that with low rates of blood flow and hyperventilation of normal alveoli this venocapillary PCO_2 gradient might be greatly elevated. In conditions which allow a high PCO_2 in the mixed venous blood and a low PCO_2 in the capillary blood which is ventilated, the effects of venous admixture will approach the effects of an equivalent degree of ventilation without perfusion (vascular obstruction) and the data would not by themselves allow differentiation. Recently, for example, subjects suffering from postinfluenzal pneumonia were shown to exhibit high a-A gradients either on the basis of uneven ventilation or caused by venous admixture from nonventilated but perfused alveoli.[4] The statement, then, that cardiorespiratory diseases other than pulmonary emboli are not associated with a significant a-A PCO_2 gradient is open to debate.

The third assumption is required if the gradient is to be used for calculating the fraction of the alveolar dead space and thereby estimating the fraction of the obstructed pulmonary arterial bed. There may well be more than one cause for the gradient observed in pulmonary embolism. The potential effect of venous admixture has already been mentioned. That this may be significant is suggested by the common finding of moderate to severe arterial desaturation in patients with acute pulmonary embolism, which is not completely corrected by 100 per cent oxygen breathing. This cannot be explained on the basis of increased alveolar dead space[3] and is characteristic of a large venous admixture component. It has been produced in dogs by experimental embolization.[5] Since acute or repeated pulmonary emboli frequently occur in subjects with a low cardiac output and hyperventilation at rest, a larger than normal pulmonary artery-pulmonary capillary PCO_2 gradient can be expected. The effects of a large venous admixture could be manifest by a significant a-A PCO_2 gradient. We know that venous admixture of severe degree can result from obstruction of a relatively small fraction of the arterial bed, thus gross misinterpretation of a gradient might occur in the presence of arterial desaturation. At present only the simultaneous measurements of venous and arterial blood gases and the a-A gradient for both oxygen and carbon dioxide tension allow the effects of nonventilation (or venous admixture) to be separated from nonperfusion (vascular obstruction).

This work is reviewed primarily to suggest possible application of physiologic data directly to clinical problems. At present the existence of a single, hopeful concept, so desirable in clinical medicine, seems threatened by the presence of multiple physiopathologic factors encountered in cardiorespiratory measurements. In the case under discussion, several assumptions are made. Existing evidence casts doubt on their validity. Failure of the first would allow a "false positive" diagnosis. Failure of the second would confuse pulmonary embolism with other clinical entities. Failure of the third would prevent the possibility of estimating the fraction of the pulmonary

REFERENCES

1. Freis, E. D., Schnapper, H. W., Johnson, R. L., and Schreiner, G. E.: Hemodynamic Alterations in Acute Myocardial Infarction, J. Clin. Invest. **31**:131, 1952.
2. Wiggers, C. J.: The Functional Consequences of Coronary Occlusion, Ann. Int. Med. **23**:158, 1945.
3. Muller, O., and Rorvik, K.: Hemodynamic Consequences of Coronary Heart Disease, Brit. Heart J. **20**:302, 1958.
4. Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegel, R. J., and Dexter, L.: Factors Regulating Pulmonary "Capillary" Pressure in Mitral Stenosis, Am. Heart J. **41**:834, 1951.
5. Soloff, L. A.: Angina Pectoris During Decubitus: Hitherto Unrecognized Manifestation of Circulatory Failure, J.A.M.A. **143**:225, 1950.
6. Paul, O.: The Use of a Mercurial Diuretic (With Theophylline) in Patients With Angina Decubitus, M. Clin. North America **35**:63, 1951.
7. Gold, H., Otto, H., Kwit, N. T., and Satchwell, H.: Does Digitalis Influence Course of Cardiac Pain? Study of 120 Selected Cases of Angina Pectoris, J.A.M.A. **110**:859 1938.
8. Marshall, F. A.: Angina Pectoris. Its Alleviation With Chlorothiazide, Am. J. Cardiol. **3**:180, 1959.
9. Baker, B. M.: Unpublished observations.
10. Viar, W. N., and Harrison, T. R.: Chest Pain in Association With Pulmonary Hypertension; Its Similarity to the Pain of Coronary Disease, Circulation **5**:1, 1952.
11. Dustan, H. P., Cumming, G. R., Corcoran, A. C., and Page, I. H.: A Mechanism of Chlorothiazide—Enhanced Effectiveness of Antihypertensive Ganglioplegic Drugs, Circulation **19**:360, 1959.
12. Ross, J. J., Waldhausen, J. A., and Braunwald, E.: Extracardiac Effects of Digitalis Preparations on Venous Return and Systemic Flow, Federation Proc. **18**:519, 1959.
13. Tobian, L., and Redleaf, P. D.: Ionic Composition of the Aorta in Renal and Adrenal Hypertension, Am. J. Physiol. **192**:325, 1958.

Announcement

A COURSE IN INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M., Dec. 7-11, 1959.

Further information and a copy of the lecture schedule may be obtained from the Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16, Ill.